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VARIATIONS IN THE TOXICITY OF CHLOROFORM FOR ANESTHESIA *

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In considering the toxicity of chloroform it is necessary to recall that a number of chemical processes are involved in its manufacture and that, in the various processes, a considerable number of chemical substances interact to give chloroform as one of the main products. Other products are formed, however, or remain from the mother substances which are used in the manufacturing process. The chloroform itself, of course, does not differ whether it be derived from acetone,[1] alcohol, methane, carbon tetrachlorid[1] or chloral, but there exist on the market many grades of chloroform, more or less contaminated with by-products of manufacture, in addition to the very best anesthetic grades freed from these products by purification, all of which are known under the general term "chloroform." Even chloroform of the anesthetic grade, however, is not pure $CHCl_3$, but contains in addition a small amount of alcohol (0.6 to 1 per cent. of 95 per cent alcohol).

It is evident from the foregoing that chloroform, which in itself could not have a variable toxicity, might, nevertheless, show such variability in even the anesthetic grades, owing to the possible presence of impurities derived either from the process of manufacture and subsequent incomplete purification or from decomposition products in a properly purified chloroform. In this connection is to be noted that pure $CHCl_3$ undergoes decomposition more rapidly than $CHCl_3$ to which a small amount of alcohol has been added, as occurs in the anesthetic grades. This introduces other factors, for, while proceeding more slowly, decomposition, especially in the presence of sunlight and air, occurs between the $CHCl_3$, alcohol and trace of water present in the alcohol.

Baskerville and Hamor[2] have made a careful study of the impurities to be found in chloroform and have divided them into two classes to

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* This investigation was undertaken at the suggestion of the Therapeutic Research Committee of the American Medical Association.

1. The most important sources of chloroform.

2. Baskerville and Hamor: Jour. Indust. and Engin. Chem., 1912, iv, 212.

indicate whether they come from the process of manufacture and improper purification or from oxidation products of pure chloroform and alcohol. Their study gives the following list of possible impurities:

A.—Excess water; excess alcohol; acetone; methyl alcohol; carbon tetrachlorid; tetrachlorethylene, hexachlorethane; aldehyds, chloral; higher alcohols and compounds; ether; acids (sulphuric, hydrochloric, formic, acetic), metallic chlorids; ethyl chlorid; ethylene chlorid; ethylidene chlorid; ethyl acetate; oils ("empyreumatic," "pyrogenous," "chlorinated"); fixed and extractive matter.

B.—Acetaldehyd; acetic and formic acids; carbonyl chlorid (phosgene); hydrochloric acid; hydrogen dioxid; chlorin; chlorin derivatives of alcohol oxidation products.

This array of possible impurities appears very formidable, although it may be stated at the outset that chloroform of anesthetic grade rarely, if ever, contains any of the impurities listed under A. Nevertheless, commercial chloroform containing some, at least, of these impurities has been used for anesthesia, so that they are of some importance. Chemical tests have been devised for their detection, however, and all chloroform intended for anesthetic purposes is subjected to such tests before being labeled "For Anesthesia."

Of more importance are the decomposition products which arise in properly purified chloroform when improperly stored. These changes arise subsequent to the time when chemical tests may be easily applied to detect their presence, since the anesthetist cannot very well make them. If they increase the toxicity of the chloroform definitely it would materially alter the present rather lax interest in the quality of the chloroform used in anesthesia.

While it is undoubtedly very desirable to use a chloroform free from all impurities and decomposition products, it has never been shown with any great degree of certainty that these substances are harmful, or at least, when present in mere traces, more harmful than pure chloroform. Such a demonstration is fraught with great difficulties, as is the estimation of the toxicity of any substance present in very small amounts in another substance, as chloroform, which in itself is markedly toxic.

Fiegel and Meier,[3] however, concluded that narcotic doses of pure chloroform had little or no action on the heart or general circulatory system and that depression of these organs arose from the impurities in chloroform. This, however, is not the current view. Schafer and Scharlieb[4] have pointed out the specific nature of the action of chloro-

3. Fiegel and Meier: Biochem. Ztschr., 1906, i, 316.
4. Schafer and Scharlieb: Jour. Physiol. Proc., 1903, xxix, 17.

form on the heart muscle, and Embley and Martin[5] have shown that such quantities in the blood as result from the administration of from 1 to 3 per cent. of chloroform vapor in air can paralyze the neuromuscular mechanism of the blood-vessels.

Of more direct bearing on the subject are the experiments of Waller,[6] who found that purified chloroform was more toxic than the concentrated impurities in chloroform. Likewise, Tunnicliffe,[7] after subjecting a good grade of chloroform to mechanical shaking and after exposing it to the direct action of sunlight, conditions under which chloroform is known to be rapidly oxidized, found that this chloroform did not differ at all from pure chloroform in its action on the heart.

Other reports such as these might be given, but the foregoing are sufficient to show that whatever the toxicity of the impurities in chloroform it cannot be very much in excess of that of chloroform, for otherwise there would not be such diametrical views.

This belief is supported also by a review of the toxic properties of the various impurities of commercial and anesthetic grades of chloroform. If one reviews the literature as to the toxic properties of the impurities given in Lists A and B, it will be found that the majority are far less toxic than a similar amount of chloroform. A considerable number, even, have been used as general anesthetics without disastrous results, although some were used in a considerably greater concentration than is considered safe with chloroform. Some are irritants only, although it is doubtful if they could possibly produce perceptible irritation if present only as mere traces. Apparently the two most toxic impurities of this sort are those which arise as decomposition products of pure chloroform, carbonyl chlorid and chlorin. It seems doubtful whether either of these could increase the harmful effects of chloroform materially, especially when considering that their dilution would be very great in anesthetic chloroform vapor.

Lehmann[8] has shown, however, that 1 part chlorin gas in 100,000 parts of air, if inhaled for some time, can cause bronchial irritation and hemorrhage and inflammation of the lungs. Likewise carbonyl chlorid, while probably not so toxic as chlorin, nevertheless has marked toxic properties, and both produce irritation of the tissues with which they come in contact. Both are said[9] to affect the anesthetist and those

5. Embley and Martin: Jour. Physiol., 1905, xxxii, 147.

6. Waller: Nature, 1907, lxxvi, 402.

7. Tunnicliffe: Pharm. Jour., xviii, 315.

8. Lehmann: Arch. f. Hyg., 1903, xlvi, 322.

9. Lee: Liverpool Med. Chir. Jour., 1895, xv, 412. Buxton: Brit. Med. Jour., 1912, i, 582.

above the patient rather than the patient himself, indicating gases lighter than air.

In view of these considerations, it seems particularly doubtful whether animal experiments would add any information indicating differences in the toxic properties of chloroform; at least, in that of anesthetic grade. Nevertheless, some experiments were undertaken, for which purpose four samples of anesthetic chloroform of different brands[10] were secured in original containers which, together with a simple of anesthetic chloroform which had been standing in the laboratory exposed to the light for at least two years in a half filled white glass bottle, comprised the series studied in this report. In the discussion of these samples they are to be identified by the numbers from 1 to 5, of which No. 5 designates the laboratory sample of chloroform.

In the first series of experiments white mice of the same lot (approximately of the same age and weight and fed on the same kind of food) were used to determine differences in the toxicity of Chloroforms 1, 2 and 3. The method was the following:

Two-liter flasks were fitted with tightly fitting stoppers through which was passed a thermometer. A mouse was placed in each of several flasks and a carefully measured amount of the chloroform in question was pipetted directly on a piece of gauze suspended inside the flask. The flask was immediately tightly stoppered and the time noted. Observations were then continuously made until the animal died, and a record was made of the symptoms observed and the time of death. The time consumed before the chloroform produced death was taken as a measure of its toxicity. Before the flasks were used again for further experiments the chloroform vapor was blown out, using compressed air. The results of these experiments are to be found in Tables 1 to 5.

It is evident from the figures in Tables 1 to 6 that wide variations occur not only in the figures of a single series, but also in the averages of the different series. Particularly is this true of the averages in Series 1, 2 and 3, but Series 4 and 5 show similar variations, although the averages are very similar. The discrepancies in the general averages of Series 1 to 3 largely disappear, however, when these are averaged, so that the difference is less marked. Accepting these final figures as only possibly correct, one has the relation of toxicity as follows:

A.	Chloroform 1	16.0
	Chloroform 2	17.5
B.	Chloroform 1	26.62
	Chloroform 3	26.92

10. Squibb & Sons, Parke, Davis & Co., Mallinckrodt Chemical Works, and Albany Chemical Company.

TABLE 1.—SERIES 1. DOSE 0.15 C.C. PER 2,000 C.C. FLASK

Mouse No.	Temperature	Time Till Death Minutes		Average Time Till Death	
		Chlor. 1	Chlor. 2	Chlor.	Minutes
25	22.5	13			
26	24.0	..	37	1	18
27	24	..	22		
28	23.5	18			
29	23	19			
30	23	..	41		
31	23	..	33	2	33.25
32	23	23			
33	23.5	17			

TABLE 2.—SERIES 2. DOSE 0.2 C.C. PER 2,000 C.C. FLASK

Mouse No.	Temperature	Time Till Death Minutes		Average Time Till Death	
		Chlor. 1	Chlor. 2	Chlor.	Minutes
19	22.5	16			
20	22	8			
21	24	6	..	1	10
22	23.5	..	8		
23	23.5	..	8		
24	23	..	10	2	8.66

TABLE 3.—SERIES 3. DOSE 0.2 C.C. PER 2,000 C.C. FLASK

Mouse No.	Temperature	Time Till Death Minutes		Average Time Till Death	
		Chlor. 1	Chlor. 2	Chlor.	Minutes
62	23.5	17			
63	23.5	34	..	1	20
64	23.5	16			
65	23	6			
69	22	35			
71	23.5	12			
66	23.5	..	11		
67	23	..	11	2	10.75
68	24	..	8		
70	23.5	..	13		

TABLE 4.—Series 4. Dose 0.18 c.c. per 2,000 c.c. Flask

Mouse No.	Temperature	Time Till Death Minutes		Average Time Till Death	
		Chlor. 1	Chlor. 3	Chlor.	Minutes
38	23	35			
41	23	27			
44	24	37			
47	23	29	..	1	28.5
50	23.5	10			
51	23.5	33			
36	23	..	44		
37	23	..	14		
40	23	..	34		
42	23	..	11	3	28.1
43	24	..	14		
45	23	..	16		
46	23	..	10		
48	23	..	47		
49	23.5	..	17		
52	23	..	47		
53	23	..	55		

TABLE 5.—Series 5. Dose 0.2 c.c. per 2,000 c.c. Flask

Mouse No.	Temperature	Time Till Death Minutes		Average Time Till Death	
		Chlor. 1	Chlor. 3	Chlor.	Minutes
54	23	30			
56	22	22			
57	22	12	..	1	24.75
61	23	35	..		
55	22	..	13		
58	23	..	30		
59	22.5	..	35	3	25.75
60	23	..	25		

TABLE 6.—Summary of Average Time Till Death, Series 1 to 5

	Chloroform		
	1	2	3
Series 1....	18.00	33.25	
Series 2....	10.00	8.66	
Series 3....	20.00	10.75	
Series 4....	28.5	.....	28.1
Series 5....	24.75	.....	25.75

Reducing these figures to a percentage basis and assuming that the most toxic of these samples when measured by the rapidity of death is 100 per cent., one obtains the following figures:

Chloroform 1	100.0
Chloroform 2	91.4
Chloroform 3	98.8

The difference in toxicity shown here of 8.6 and 1.2 per cent. cannot be accepted as absolute differences since these figures were derived from general averages, the individual figures of which varied so widely. They seem more than merely the result of chance, however, and it seemed advisable to continue these experiments along somewhat different lines, using a much larger number of animals, so that the law of averages would more surely hold good.

TABLE 7.—AVERAGE TIME TILL DEATH OF FISH

Sample	1	2	3	4	5
Series 3....	66	77	85	48	69
Series 4....	94	149	143	85	97
Series 5....	97	119	152	166	142
Series 6....	148	77	94	141	110
Series 7....	85	122	123	115	92
Series 8....	158	141	197	206	178
Series 9....	157	170	155	99	148
General average	115.0	122.1	137.0	122.8	119.3

TABLE 8.—PERCENTAGE OF DEATH IN FISH EXPERIMENT

Sample	1	2	3	4	5
Series 3....	100	80	90	80	70
Series 4....	60	60	60	60	70
Series 5....	30	70	80	80	80
Series 6....	100	80	80	90	90
Series 7....	70	90	90	80	60
Series 8....	80	70	80	70	60
Series 9....	60	40	70	80	90
Average ...	71.4	70.0	78.6	77.1	74.3

A further series of toxicity experiments was devised, small trout being used instead of white mice. In these experiments a measured amount of the chloroform to be tested was dissolved in water of a constant temperature, the chloroform being dissolved by agitation with the water in a glass-stoppered measuring flask of appropriate size.

A suitably diluted chloroform water after having been prepared in this way, was poured into large glass jars and a lot of ten fish added by lifting them from the storage tank in a dip net. In all cases, all the chloroforms under examination were tested at the same time by allowing an interval of thirty seconds to intervene between each transfer of a given lot of fish to the chloroform water. At varying periods of from twelve to forty minutes thereafter the fish were again transferred with the dip net from the chloroform water to fresh tap water and the time was noted when the fish stopped breathing, as indicated by the cessation of gill movements. This was taken as one of the indications of toxicity. The other indication was the survival or death of the fish of each lot. At first, dilutions of 1 part chloroform to 2,500 parts water were tried, but this was found to be too toxic, and later, dilutions of 1 part to 8,000 to 10,000 parts water were found to prolong the intoxication sufficiently for accurate observation. The results of seven series of such experiments with Samples 1 to 5, involving 350 fish, are to be found in Tables 7 and 8, in which are given the average time till death of such fish as were killed and also the total number of dead in each lot. Temperatures and the length of time the fish were in the chloroform water are not given, but were always constant with the five samples of chloroform for an entire series.

It will be seen from these tables that here, as in the earlier experiments on mice, wide variations are to be found in the figures of individual experiments. Eliminating the results of time till death,[11] however, it is noticeable that the differences in the toxicity of the various samples of chloroform are not marked, especially when considering the wide variations in individual experiments in which the order of toxicity is different for every series. It must be concluded on this account, then, that this method does not lend itself to a determination of the extremely slight differences, if any, in the toxicity of anesthetic grades of chloroform. This is especially emphasized by the result with Chloroform 5, the laboratory sample of chloroform 2 years old, which occupied an intermediate place in its toxicity, although it would be presumed that this sample would possibly be the most toxic of the five samples.

A final series of experiments on trout was carried out to determine whether the toxicity of chloroform could be accentuated by fractional distillation. Samples 1 and 5 were chosen for these tests. Each was distilled so that three fractions were obtained as follows: below 60 degrees, Samples 1_1 and 4_5; between 60 and 61 degrees, Samples 2_1 and

11. It seems advisable to eliminate these figures in estimating the toxicity of a given chloroform as this is not nearly so important as the fact of death itself in measuring toxicity. These figures have been introduced into this and a later table merely to show the lack of relationship between them.

5_5; above 61 degrees, Samples 3_3 and 6_6. The middle fraction, between 60 and 61 degrees, was in both cases the largest part of the distillate. The manner of making the dilutions and of experimentation were the same as in the preceding series. The results are to be found in Tables 9 and 10.

TABLE 9.—AVERAGE TIME TILL DEATH IN FINAL EXPERIMENTS ON TROUT

Sample	1_1	2_2	3_3	4_4	5_5	6_6
Series 1....	132	139	163	...	....	119
Series 2....	123	...	98	117	125	88
Series 3....	59	65	84	76	79	
Series 4....	...	90	...	98	97	77
Average	104.6	98.0	115.0	97.0	100.3	94.6

TABLE 10.—PERCENTAGE OF DEATH IN TROUT

Sample	1_1	2_2	3_3	4_4	5_5	6_6
Series 1....	70	70	60	..	..	70
Series 2....	70	..	90	90	100	90
Series 3....	90	80	80	80	80	
Series 4....	..	70	..	70	80	90
Average	76.6	73.3	76.6	80.0	86.6	83.3

TABLE 11.—PERCENTAGE OF TOXICITY OF CHLOROFORM

	Chloroform				
	1	2	3	4	5
Mice	100.0	91.4	98.8		
Trout	100.0	98.0	110.1	107.9	104.0
Trout distillates....	100.0	.....	....	....	110.3

In this series of experiments also, there is no relation between the time till death and the percentage of deaths even in the general averages. Taking the percentage of death as a criterion of toxicity, however, it appears that Distillate 2_1, 60 to 61 degrees is the least toxic among the distillates from Sample 1, whereas the similar Distillate 5_5, 60 to 61 degrees, is the most toxic of the distillates from Sample 5, 13.3 per cent. more deaths resulting from the latter.

Another fact developed is that the average toxicity for the distillates from Sample 1 is 75.5 per cent.; for those from Sample 5 it is 83.3 per cent., a difference of 7.8 per cent. This becomes particularly interesting when it is noted that the difference between the original chloroforms before distillation was only 2.9 per cent. This indicates an error of 4.9 in the percentage of deaths and shows that, in spite of the wide variations in single experiments, the method gives reasonably accurate results. It also shows, inasmuch as the differences in the percentage of deaths between the various samples of chloroform were found not to exceed 8.6 per cent., that there cannot be said to be any certainly demonstrable difference in the toxicity of these samples, for errors in results would easily account for the differences found.

A comparison of the toxicity of the five samples of chloroform as obtained in the three different methods of experimentation, on the basis that the toxicity of Chloroform 1 equals 100 per cent., is given in Table 11.

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THE RELATION OF THE PURGATIVE ACTION OF MAGNESIUM SULPHATE TO PERISTALSIS, AND THE GENERAL LAW OF CROSSED INNERVATION *

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While the subject I intend to discuss in particular is the inhibitory rôle of magnesium salts in its relation to the production of intestinal peristalsis, my chief object is to set forth certain general views I hold now, and have held for many years, on the subject of inhibition in general and the rôle which it plays in the mechanism of all sorts of movements in the animal organism. I shall begin the discussion of the relation of magnesium salts to peristalsis by calling attention to two sets of facts which seem to contradict each other.

It is a well-known and well-established fact that magnesium sulphate, or Epsom salts, is one of the most efficient purgatives. There have been many discussions as to the cause of the action of saline purgatives. According to one view, which has undergone many variations in its details, the cause of the purgation consists in the power of the saline to bring about an accumulation of liquid within the lumen of the intestine. We need not discuss here the nature and origin of this liquid. For our purpose it suffices to say that no matter from what cause liquid accumulates within the intestine, its mere presence would not cause purgation without the mediation of peristaltic movements of the intestinal canal. It is a known fact that the presence of large quantities of liquid within a paralyzed intestine does not lead to evacuation. According to another view which in recent years has been brought forward again by pupils of Jacques Loeb, the cause of action of certain purgative salts consists directly in their ability to stimulate the neuromuscular apparatus of the peristaltic mechanism. According to all views, then, peristaltic movements are indispensable for purgation, and therefore magnesium sulphate as an efficient purgative is expected to increase, or at least not to inhibit, the peristaltic movements of the intestines. I hardly need add that under the term peristalsis is generally meant a progressive movement of a vermiform character, which

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* From the Department of Physiology and Pharmacology of the Rockefeller Institute for Medical Research.

in our special case, means a vermiform movement of the gastro-intestinal canal running in an aboral direction.

Now in apparent opposition to the mentioned fact, I have to enumerate a number of observations which were safely established in our laboratory in the course of the last few years. In experiments carried out by Auer and myself several years ago, in which the behavior of the intestines of rabbits was observed in a warm bath of normal saline, we found that intravenous injections of magnesium salts stop peristaltic movements promptly. Usually not much peristaltic movement of the intestines can be seen, when the abdomen of a rabbit is opened. In order to observe the effect of magnesium sulphate, peristaltic movements had to be brought on by artificial means: by intravenous injections of sodium sulphate, barium chlorid, physostigmin or ergot, or by the destruction of the spinal cord. The peristaltic movements brought on by these means were sometimes of a violent character. All these peristaltic movements were either completely inhibited, or at least greatly reduced, by an intravenous injection of a solution of magnesium sulphate (or magnesium chlorid). In a later series of experiments, carried out by Don R. Joseph and myself, a method was employed in which the peristaltic movements could be studied in animals whose abdomens were closed. At one sitting the abdomen of rabbits was opened under proper anesthesia, and catheters, bearing at one end a small balloon, were inserted into the lower part of the duodenum and into the stomach; stomach, duodenum and abdomen were then properly closed. In the following days the protruding end of each catheter was connected with a graphic apparatus and tracings representing the peristaltic movements of the stomach and the duodenum were obtained. There were in nearly all cases good, spontaneous movements of the stomach and the duodenum. We have, then, established beyond a doubt that the action of magnesium sulphate on the stomach and the duodenum is, under all circumstances, only of an inhibitory character. Whether the peristaltic movements were spontaneous in origin, or were brought about or intensified by barium chlorid or other substances, an intravenous injection of magnesium sulphate, even in an isotonic concentration, invariably caused an immediate inhibition, or at least an unmistakable reduction, of the persistalsis, lasting for some time after the injection has ceased.

These experimental results were obtained, as I stated before, by intravenous injections of the magnesium salts. I am now in a position to state, however, that the same inhibitory results can be readily obtained when the magnesium solutions are introduced into the lumen of the intestine. Auer and I found that magnesium salts, when introduced into the lumen of the intestine, are readily absorbed and may

cause respiratory paralysis and death of the animals within a short time after the injection. Recently I have studied the effect of such a direct introduction of magnesium salts into the lumen of the intestine on the behavior of the peristaltic movements of the latter. I found that the intestine becomes practically paralyzed. I shall mention here one striking result. When the trachea of an animal is clamped and the animal thus killed by asphyxia, the exposed intestines show more or less strong peristaltic movements. When, however, a solution of magnesium salts is previously introduced into the lumen of the intestine, no part of the gastro-intestinal canal shows movements worth mentioning during or after the asphyxia.

These various experimental observations show unmistakably that magnesium salts, whether given intravenously or introduced into the lumen of the intestine, not only do not cause any peristalsis of the intestine, but positively inhibit it, when it is present. The puzzling question which now presents itself is this: If magnesium sulphate causes a suppression, an inhibition of the peristaltic movements, and only an inhibition, how can it bring on purgation in which, as we have seen above, peristaltic movement of the intestine is an indispensable factor?

To answer this question I shall have to enter into an analysis of inhibition and the rôle it plays in peristalsis. All know what is meant by inhibition. The best known type of it is the phenomenon with which all are acquainted; it is the fact that the stimulation of the end of the vagus which goes to the heart stops the beating of that organ. The heart is a muscle. A nerve going to a muscle we usually term a motor nerve. Stimulation of such a nerve causes contraction of the muscle pertaining to it. But stimulation of the end of the vagus which goes to the heart stops the heart from beating. That is inhibition. Numerous other examples and other forms of inhibition are now well known. One of them is, that stimulation of the end of the splanchnic nerve which goes to the intestines, stops peristalsis of the intestine; it inhibits the peristalsis. Here we have some evidence that the phenomenon of inhibition may be connected with the peristalsis of the intestines. However, the most striking fact that inhibition is actually concerned in the peristaltic movements of the digestive tract was made by us thirty-four years ago in our studies of the function of deglutition. We then first established that after each beginning of a deglutition various parts of the esophagus develope a peristalsis at various intervals, according to their distances from the tongue and pharynx. For instance, the peristalsis of the cervical part of the esophagus sets in about two seconds after the beginning of deglutition; the esophagus in the upper part of the thorax begins to contract about three seconds, the part of the esophagus above the diaphragm begins to contract about six

seconds, after the deglutition. These data were obtained from observations on my own esophagus. We discovered in the course of these studies that, when the deglutitions are repeated, say in less than every three seconds, the upper part of the thoracic esophagus does not contract after each deglutition, but only after the last deglutition has taken place. The same applies for the cervical as well as the lower part of the esophagus. In other words, with each deglutition which sends down an impulse for a contraction of the peristalsis, also an inhibitory impulse is sent down along the esophagus—for the purpose of inhibiting any possible contraction which may be present in any part of the esophagus, due to a previous act of deglutition. I may say here that each deglutition inhibitis also the presence of a tonus in the esophagus. This physiological phenomenon reminds one of the precautions which are taken when an express train is sent off; along the entire road telegraphic messages are sent, to keep the tracks free. That is the sense of the inhibitory wave which runs ahead of the peristaltic contraction to keep the track free.

Some thirty years ago I tried to generalize this point of view, to apply it to all functions of the body which require definite movements. I stated then, that, for instance, for the extension of the leg it is necessary that the flexors should be inhibited from being contracted simultaneously, or from remaining in a state of tonus. At that time I illustrated the actual occurrence of such antagonistic relations by the behavior of the function of respiration; during each inspiration the contraction of the expiratory muscles is inhibited, and during each expiration the diaphragm and other inspiratory muscles are suppressed, inhibited.

I wish to dwell a little longer on that subject. You probably know that these relations of flexors and extensors, as I anticipated them many years ago, have been brilliantly studied since 1895 by Sherrington, who terms the relations of flexors and extensors "reciprocal innervation." That designation is for these specific relations proper enough, because just as the flexors become inhibited, when the extensors have to contract, the extensors also become inhibited when the flexors are contracting. It is, then, a truly *reciprocal* innervation process. But when we apply these relations to a canal in which movements go on only in one direction, there is, of course, only one-half of this process. It is always only the lower part of the canal which has to be relaxed, when the upper part is contracting. A true antiperistalsis does not exist. In order to comprise all these phenomena under one head, I term the relations under discussion as "contrary innervation." It produces simultaneously a contraction in one part and an inhibition in another — in the contrary part. That means, two parts which are

concerned in a single function are simultaneously innervated in a contrary way. The upper part of the canal is contracting in order to move the contents downward and the lower part is relaxing in order to remove any obstacle to this motion.

We shall now turn back to the digestive tract. I shall mention here first that, on the basis of these considerations, we discovered long ago that with each act of deglutition the tonus of the cardia becomes inhibited—to open the gate into the stomach for the entrance of the contents which are swallowed down. In recent years Joseph and I found that during each contraction of the pyloric part of the stomach an inhibition of the movements of the duodenum takes place. Cannon and Lieb found that during a peristaltic contraction of the esophagus a simultaneous relaxation of the stomach makes its appearance. Finally, Lyman has observed that the colon becomes motionless and relaxed while the material is driven through the ileocolic sphincter by peristalsis in the ileum. All these observations have evidently that one background in common, namely, that for the purpose of moving downward the contents of the gastro-intestinal canal, the distal part of the various sections of the canal become inhibited, while the adjoining proximal (upper) part of the corresponding section gets into a state of contraction — a manifestation of the Law of Contrary Innervation.

Of greater interest to our problem is the instructive observation which was made by Bayliss and Starling some seventeen years ago, namely, that a stimulation of the intestines at any place causes a contraction above the point of stimulation and a relaxation or inhibition of the part of the intestine below the point of stimulation. Bayliss and Starling called this phenomenon the Law of the Intestines. But it is evident that this phenomenon is the law not only of the intestines, but of the entire digestive canal and that it is, furthermore, a part of the phenomenon which I term "Contrary Innervation."

The outcome of the foregoing facts under consideration, bearing on the intestinal peristalsis, is evidently this: A peristaltic movement does not consist merely in a vermiform downward moving contraction; peristalsis is made up of two simultaneous phenomena: a contraction of the upper part and a relaxation or an inhibition of the lower part of the section of the gastro-intestinal canal, engaged in the act of moving downward some of its contents.

Bayliss and Starling have shown that this dual response of the intestine to a single stimulus takes place even when the intestines are freed from their extrinsic innervation. They thought that the process is of a myogenic origin; but Magnus has shown conclusively that it is connected with Auerbach's plexus, the myenteric plexus, located between the longitudinal and circular sheaths of the fibers of the intes-

tinal muscularis. We may, therefore, formulate our conclusion in the following terms: A stimulation of the myenteric plexus produces simultaneously a double effect, a contraction of the muscle fibers above, and an inhibition of any contractions below the point of stimulation.

I shall now turn my attention to the relation of magnesium sulphate to the phenomenon of inhibition. About sixteen years ago, when studying the effect of intracerebral injection of various salts, I came across the following surprising fact: While the injection into the cerebrum of many other salts produced characteristic convulsions, the injection of a few drops of a 5 per cent. solution of magnesium sulphate caused the rabbit to turn over on one side and remain lying in a state of stupor and relaxation. With a long standing interest in the phenomenon of inhibition it was quite natural for me to interpret the stuporous and relaxed condition of the animal as possibly being a state of inhibition. In the many studies of the action of salts on the animal organism to be found in the physiological and pharmacological literature, the effects observed and studied were always those of the exciting action of the salts. It was from the point of view that possibly the magnesium ion in the body is chiefly concerned in the inhibitory processes, that we started our various studies on the effects of magnesium. It became a working hypothesis; we had not yet come across some definite, weighty facts which are capable of disproving this hypothesis. As to the relations of magnesium salts to the gastrointestinal canal, it has been stated before, that in the studies of Auer, Joseph and myself no other effect was found but that of inhibition of the peristaltic movements of the intestine.

We come now to our original question; it is this: On the one hand, it is certain that magnesium salts cause purgation, a process in which peristalsis must be a factor; on the other hand, the extensive experimental studies revealed the unmistakable fact that magnesium salts inhibit intestinal peristalsis. How can we reconcile these apparently contradictory facts? My answer to this question, given merely in a general way, is this: 1. The phenomenon of peristalsis does not consist alone in a contraction of a certain part, but in a contraction of the proximal and *relaxation of the distal part* of a section of the intestine. 2. The effect of magnesium sulphate on peristalsis may consist chiefly in its relation to the inhibitory part of the phenomenon of peristalsis.

As I have just indicated, my answer to the central question shall be of a general character; I am unwilling for the present, to enter on definite statements as to how magnesium affects the peristalsis. I am confident that details which I may venture to state now will have to be modified by facts which future experimental investigations are sure to bring to light. I shall, however, try to continue the analysis by dis-

cussing briefly a few points which may have some bearing on the subject.

1. We have seen above that a stimulation of any part of the intestine causes by means of the intrinsic myenteric plexus (and probably also by the aid of the extrinsic innervation), a contraction above and a relaxation below. How strong the contraction of the part above may be and how intense is the inhibition of the part below, and how far it may extend, depends on a variety of circumstances. In the first place, we must here, as everywhere, distinguish between *irritability* and *stimulation*. Increase of irritability alone can bring out no action without the incident of a stimulus. The irritability of the concerned innervation may be low or high and may concern the exciting and inhibitory phases in various degrees. For instance, magnesium salts may increase exclusively or essentially the irritability of the inhibitory phase, while other salts, for instance, sodium sulphate, may increase preferably or exclusively, the irritability of the exciting phase. There is good reason for the assumption that the increase of irritability occurs through the circulation; but we have no definite evidence that this may not occur also by mere action on the periphery.

Again, stimulation may affect preferably the exciting phase or the inhibitory. But we are rather inclined generally to assume that a stimulus affects, as a rule, both the exciting and the inhibitory phases simultaneously. We are also inclined to assume that the point of attack of a stimulus is to be found at the periphery. But there is no evidence against the assumption that stimulation may take place also directly through the circulation. We need hardly add that a stimulus may be weak or may be strong.

Taking all these points together, it can be seen at a glance how variable the effects of some substances on the intestine may be. With a low irritability of certain sections of the intestine, and with a comparatively low stimulus from the periphery, the effect may be altogether circumscript, and the result may be, not peristalsis, but only "segmentation," the effect of each stimulus not being an intense contraction above and not an extensive relaxation below. With an increased irritability and with a moderately strong stimulus, there may be a fair contraction above and a fairly extensive relaxation below, and the result will be a persistalsis extending over a fairly large section. With a strongly increased irritability of both phases and with a strong stimulus, the result may be a rapid peristalsis, running through the entire intestine within a very short time, a condition which we termed "peristaltic rush."

2. A brief discussion of peristaltic rush will not be amiss here. As was just stated, by "peristaltic rush" we designate the phenomenon of a rapid peristaltic movement runing downward through the entire small intestine within a fraction of a minute. This phenomenon was observed for the first time by Van Bram-Houckgeest some forty years ago in rabbits dying from asphyxia. He termed it *Rollbewegungen*. Several years ago Auer and I succeeded in producing this phenomenon practically at will in living rabbits. The method we used consisted in injecting intravenously antagonistic substances; that is, one substance which favors contractions of the gut, and another which favors the inhibition of such contractions; for instance, ergot and magnesium sulphate.

3. Our experimental studies of the inhibitory effect of magnesium salts on peristalsis were made either by administering magnesium sulphate intravenously or by injecting it into the lumen of the small intestine. However, when administering magnesium sulphate by mouth (as for the purpose of purgation), while the salt passes through the stomach it meets with sodium chlorid and some carbonates. It is therefore possible, and even probable, that parts of the magnesium sulphate become converted into sodium sulphate and magnesium carbonate. Sodium sulphate is soluble and is readily absorbed. From the experiments of MacCallum and of Auer we know that sodium sulphate when given intravenously is apt to bring on some peristalsis. Magnesium carbonate is not soluble and remains within the intestine probably entirely unabsorbed. We know that magnesium carbonate is capable of acting as a purgative. The insoluble carbonate acts possibly within the intestine in two ways: on the one hand, it attracts liquid into the lumen of the intestine thus distending it, and, on the other hand, the carbonate is likely to serve as a chemical stimulus directly on the mucosa. At any rate, it is not impossible that that part of the magnesium sulphate which has been converted into a carbonate acts within the intestine as a stimulus calling forth peristaltic movements. On the other hand, the part of the magnesium sulphate which is converted into sodium sulphate may be the means of increasing the irritability of the exciting phase of the peristalsis; it may serve also as a stimulus to the neuromuscular apparatus. The remaining unconverted portion of the magnesium sulphate increases the irritability of the inhibitory phase of peristalsis. Now we have seen above that by the administration of antagonistic substances, that is, substances, one of which increases the exciting phase, while the other increases the inhibitory phase of peristalsis, are capable of calling forth a "peristaltic rush," that is, a peristaltic wave which runs rapidly through the entire small intestine within a short time. We can therefore easily conceive that the

purgative action of magnesium sulphate, when administered by the mouth, results from the fact that a part of it acts by increasing the inhibitory phase of peristalsis, while other parts, by being converted partly in sodium sulphate and partly into magnesium carbonate, increase the irritability of the exciting phase of peristalsis and serve as an inciting stimulus to start peristaltic movements. The result is the development, after some time, of partial and perhaps complete peristaltic rushes.

I wish to repeat again that I offer this detailed analysis of the action of magnesium sulphate merely as a preliminary hypothesis. Future experimental work will throw more light on these questions.

4. In a few words, my general conception of the various effects which may result from the simultaneous actions of exciting and inhibitory factors on the functions of the animal body are as follows: The resultant effects of the antagonistic actions can be of a threefold nature which may be designated as *tonus, rhythm* and *peristalsis.*

1. The resultant effect of the antagonistic actions may be *manifest at the same place and at the same time.* This is a *tonus.* The degree and the character of the tonus depend on the preponderance of one or the other factor.

2. The effect of both antagonistic factors may be *manifest at the same place, but at different, alternating times.* It is then a *rhythm;* contraction alternates with inhibition.

3. Both effects of the antagonistic factors may be present *at the same time, but manifest themselves simultaneously in different* parts. The resultant is then, as far as the intestines and other muscular tubes are concerned, a *peristalsis;* a contraction above and an inhibition below.

STUDIES IN RENAL FUNCTION WITH SPECIAL REFERENCE TO NON-PROTEIN NITROGEN AND SUGAR CONCENTRATION IN THE BLOOD, PHENOLSULPHONEPHTHALEIN ELIMINATION AND BLOOD PRESSURE *

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Until the theories of nephritis are reduced to one and until that one has been conclusively proved to be correct, continued investigations, both clinical and experimental, seem to be demanded.

These studies in nephritis deal on the one hand, with the accumulation or retention in the blood of the end-products of protein metabolism and glucose concentration in the blood, and on the other hand, with the functional capacity of the kidneys in so far as the latter may be determined by the elimination of phenolsulphonephthalein. In short, the purpose of this paper is to study:

1. The relation of protein feeding to nitrogen retention in the blood.
2. The relation of nitrogen retention to renal function.
3. The relation of blood-sugar, blood-pressure, phenolsulphonephthalein elimination and nitrogen retention.

So far as we can ascertain, there have been no studies covering all of these phases simultaneously and the possible relationship existing between them; though quite recently Folin[1] and Frothingham and Smillie[2] have reported on somewhat similar studies, the latter presentation having been published shortly before the completion of this work.

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1. Folin, Otto, Denis, W., and Seymour, Malcolm: The Non-Protein Nitrogen Content of the Blood in Chromic Vascular Nephritis (Arteriosclerosis) as Influenced by the Level of Protein Metabolism, THE ARCHIVES INT. MED., 1914, xiii, 224.

2. Frothingham, Channing, and Smillie, Wilson, G.: The Relation Between the Phenolsulphonephthalein Excretion in the Urine and the Non-Protein Nitrogen of the Blood in Human Cases, THE ARCHIVES INT. MED., 1914, xiv, 541.

I. THE RELATION OF PROTEIN FEEDING TO NITROGEN RETENTION IN THE BLOOD

With but two exceptions, these observations were made on ward patients in the University Hospital on the service of Dr. Alfred Stengel.

To study the effect of the level of protein diets on the retention of nitrogen in the blood, we first placed the patient on a diet of about 2,300 calories, which represented approximately 5 gm. of nitrogen; then on a diet of 2,150 calories, corresponding to 12 gm. of nitrogen, and finally, on a diet of 2,300 calories or about 18 gm. of nitrogen.

TABLE 1.—INFLUENCE OF PROTEIN FEEDING ON RETENTION OF NITROGEN IN BLOOD IN CARDIORENAL DISEASE

Case	Diagnosis	Age	Sex*	Date	Nitrogen per hundred c.c. of blood, mg.		
					Low Protein Diet	Ward Diet	High Protein Diet
1. J. H. B.	Chronic nephritis; chronic endocarditis	39	♂	4/1	23	18	30.8
2. J. McW.	Chronic nephritis; chronic myocarditis	48	♂	4/1	28	28	35.5
3. J. H.	Chronic interstitial nephritis; chronic myocarditis	34	♂	4/1	....	28	33.6
4. J. W.	Chronic nephritis; chronic myocarditis	45	♂	4/2	26	28	
5. H. L.	Chronic interstitial nephritis; myocardial weakness; arteriosclerosis	75	♂	5/9	26	32	39
6. A. P.	Chronic nephritis; chronic myocarditis	49	♂	5/9	30	36	39
7. L. S.	Chronic interstitial nephritis; myocardial weakness	55	♀	7/21	23	30	37
8. S. C.	Arteriosclerosis.....	70	♀	7/21	18	29	35
9. F. G.	Chronic nephritis; chronic myocarditis; asthma	49	♀	10/19	29	28	

* In this and the following tables, ♂ denotes male, and ♀ female.

The duration of each period was three days, and in the afternoon of the third day the blood was withdrawn from a vein in the arm and analyzed according to the recent method of Folin and Farmer[3] with the modification that the ammonia liberated was collected in standardized fiftieth normal sulphuric acid and titrated with fiftieth normal sodium hydroxid. It is generally conceded that by this method normal values are those with a total nitrogen of less than 30 mg. per hundred c.c. of blood. We found that all but two cases revealed higher figures at the end of the high protein diet, as will be seen in Tables 1 and 2,

3. Folin, O., and Farmer: Jour. Biol. Chem., 1912, xi, 527.

which are good illustrations of the influence of protein feeding on the retention of nitrogen in nephritics.

In several cases of pure nephritis of the chronic interstitial type and in which there was an increase in non-coagulable nitrogen on a low protein diet, there was a striking reduction in tolerance for an increasing amount of proteid, as was shown by the marked rise in retention products as well as by nausea and vomiting in a few cases (Table 2). Clinically, these results indicate not only the importance of a low proteid diet in certain types of nephritis, but they also illustrate the advantages of this test for a more accurate diagnosis of these types.

TABLE 2.—Rise in Retention Products Following Increase in Protein Ingestion in Cases of Chronic Interstitial Nephritis

Case	Diagnosis	Age	Sex*	Date	Nitrogen per hundred c.c. of blood, mg.		
					Low Protein Diet	Ward Diet	High Protein Diet
1. W. P.	Chronic interstitial nephritis	65	♂	4/1	26	33	40
2. L. L.	Chronic interstitial nephritis	55	♀	4/1	29	30	32
3. D.	Chronic interstitial nephritis	55	♀	4/9	43	54	60
4. G. C. B.	Chronic interstitial nephritis	40	♂	2/26	28	25	43
5. M. W.	Chronic interstitial nephritis	28	♀	5/4	43	35	
6. Mr. R.	Chronic interstitial nephritis	27	♂	6/15	67	88	92
7. S. R.	Chronic interstitial nephritis	26	♂	6/28	56		
8. E. B.	Chronic interstitial nephritis	43	♂	7/6	30	40	56
9. E. H.	Chronic interstitial nephritis	21	♀	7/7	22	29	37
10. P. P.	Chronic interstitial nephritis	61	♂	6/13	29	33	42
11. M. L.	Chronic interstitial nephritis	53	♀	10/1	36	37	
12. S. B. J.	Chronic interstitial nephritis	43	♂	11/27	50		

In fact, observations on nitrogen retention are becoming more and more frequent in the literature. Macwitz, Rosenberg and Tscherkoff,[4] in an exhaustive study of the pathology of nephritis and its functional diagnosis by various tests, conclude that nitrogen retention is indicative of vascular disease and that, in chronic cases, it is a good index of the degree of insufficiency and gives a valuable clue for both prognosis and therapy.

With regard to the influence of chronic passive congestion on nitrogen retention in the "cardiorenal" symptom-complex, our results

4. Macwitz, Rosenberg and Tscherkoff: München. Med. Wchnschr., 1914, No. 23, p. 1268.

TABLE 3.—Result of Examination of a Series of Cardiorenal Cases

Case	Diagnosis	Age	Sex	Blood Nitrogen Mg. per 100 c.c. of Blood	Blood Sugar Gm. 100 c.c. of Blood	Phthalein Elimination % in 2 Hrs.	Blood Pressure	Eye-Grounds	Edema	Liver*	Albumin	Casts	Sp. Gr.
1. J. H. B.	Chronic nephritis; chronic endocarditis	39	♂	23	0.07	10	110/60	.....	++	10	+	+	1.007
2. J. McW.	Chronic nephritis; chronic myocarditis	48	♂	28	0.076	40	135/98	.....	++	4	++	++	1.025
3. J. H.	Chronic interstitial nephritis; chronic myocarditis	34	♂	28	0.085	40	190/130	Early sclerosis	++	10	+	+	1.015
4. J. W.	Chronic nephritis; chronic myocarditis	45	♂	26	0.09	45	138/70	.....	++	4	++	++	1.021
5. H. L.	Chronic interstitial nephritis; myocardial weakness; arteriosclerosis	75	♂	26	0.131	30	155/90	Indentation of veins. Arteries thickened	—	5	+	+	1.015
6. A. P.	Chronic nephritis; chronic myocarditis	49	♂	30	0.159	15	150/99	.....	+	4.5	++	++	1.025
7. L. S.	Chronic interstitial nephritis; myocardial weakness	55	♀	23	.....	25	155/86	Moderate sclerosis	+	1.5	+	—	1.017
8. M. C.	Chronic interstitial nephritis; chronic myocarditis	41	♀	28	0.09	8	158/105	Incipient sclerotic changes	+	6	++	+	1.013
9. F. G	Chronic nephritis; myocarditis; asthma	49	♀	28	0.153	33	200/130	Normal.....	+	?	++	++	1.021
10. B. J. B.	Chronic nephritis; myocardial weakness	65	♂	67	.....	30	160/70	.....	++	10	++	++	1.019

* Centimeters below costal border in midclavicular line.

TABLE 4.—Result of Tests in Cases of Chronic Interstitial Nephritis with Hypertension

Case	Diagnosis	Age	Sex	Blood Nitrogen Mg. per 100 c.c. of Blood	Blood Sugar Gm. 100 c.c. of Blood	Phthalein Elimination % in 2 hrs.	Blood Pressure	Eye-Grounds	Albumin	Casts	Sp. Gr.
1. W. P.	Chronic interstitial nephritis	65	♂	26	0.120	35	180/130	.....	+	+	1.025
2. L. L.	Chronic interstitial nephritis	55	♀	39	0.082	43	225/110	.....	+	+	1.021
3. D.	Chronic interstitial nephritis	55	♂	43	0.106	.	210/150	.....	+	+	
4. G. C. B.	Chronic interstitial nephritis	40	♂	43	0.075	48	185/136	.....	+	+	1.015
5. M. W.	Chronic interstitial nephritis	28	♀	43	0.123	10	256/168	.....	++	+	1.013
6. Mr. R.	Chronic interstitial nephritis	27	♂	67	0.117	18	210/130	.....	++	++	1.009
7. S. R.	Chronic interstitial nephritis	26	♂	56	0.123	22	205/150	Disks edematous. Hemorrhages	++	++	1.013
8. E. B.	Chronic interstitial nephritis	43	♂	46	.....	16	155/110	.....	+	+	1.014
9. E. H.	Chronic interstitial nephritis	21	♀	35	0.07	40	210/115	Edema. Veins full and dark. Patches of exudate	+	+	1.008
10. P. F.	Chronic interstitial nephritis	61	♂	39	0.074	24	190/110	Neuritis, hemorrhages, sclerosis	++	++	1.019
11. M. L.	Chronic interstitial nephritis	53	♀	36	0.082	37	170/135	Vessels sclerotic. Senile choroidal changes	+	+	1.013
12. C. B.	Chronic interstitial nephritis	40	♀	....	0.146	10	250/150	Retinitis. Hemorrhages	++	++	1.015
13. B. W.	Chronic interstitial nephritis	22	♀	33	0.085	60	205/170	Sclerotic changes....	+	—	1.009
14. S. B. J.	Chronic interstitial nephritis	43	♂	50	0.088	37	242/152	Marked sclerosis....	+	+	1.017
15. McC.	Chronic interstitial nephritis	66	♂	58	0.08	75	178/95	Veins full. Hemorrhagic exudation	+	++	1.021

confirm those of Rowntree and Fitz,[5] in that there is practically no increase in waste nitrogenous products provoked by such congestion per se; although Strauss and Hohlweg[6] state that this factor is responsible for a moderate increase in these products. See Tables 1 and 3.

In our series of cardiorenal cases, in many of which chronic passive congestion was very evident, only one presented a rise in blood nitrogen. To be of real value in therapy and prognosis, we believe that the test should be repeated at intervals, that due consideration should be given the time and the amount of protein intake, and finally, that each test should be accompanied by a determination of the phenolsulphonephthalein elimination. When both the clinical picture and these details are observed, the value of the test cannot be disputed.

In Table 3, it will be noted that of the cardiorenal group investigated, the absence of retained nitrogen is striking when contrasted with Table 4, in which cases of pure chronic interstitial nephritis with hypertension are considered. In the latter group, eleven out of fourteen cases show evidence of retention, and it is this same group in Table 2 which illustrates a marked reduction in tolerance for proteins as noted above. Certain it is that excessive amounts of nitrogen in the blood afford an index of renal functional capacity. The significance of these results in the pure nephritic cases, however, both from the prognostic and therapeutic point of view, will be dealt with later.

II. THE RELATION OF NITROGEN RETENTION TO RENAL FUNCTION AS DETERMINED BY THE PHENOLSULPHONEPHTHALEIN ELIMINATION

The technic of the phenolsulphonephthalein test used was that originated by Rowntree and Geraghty.[7] Before discussing the results in our three groups of cases, it may be advisable to note certain conditions under which marked variations in the phthalein output occur. These are:

1. Chronic passive congestion.
2. Various stages of nephritis.
3. Hyperpermeability.

1. *Chronic Passive Congestion.*—Several workers have shown that marked chronic passive congestion greatly decreases the phenolsulphonephthalein output and that as the circulation improves, the output

5. Rowntree, L. G., and Fitz, R.: Studies of Renal Function in Renal, Cardiorenal and Cardiac Diseases, THE ARCHIVES INT. MED., 1913, xi, 258.

6. Strauss and Hohlweg: Quoted by Rowntree and Fitz, THE ARCHIVES INT. MED., 1913, xi, 278.

7. Rowntree and Geraghty: Jour. Pharm. and Exper. Therap., 1910, i, 579.

rises if there is no coexisting renal involvement.[8, 9] This fact may well be utilized in determining the relative responsibility of heart or kidney in the troublesome symptom complex, cardiorenal disease, as successful therapy in this condition rests largely on our knowledge of the underlying causative factor.

2. *Various Stages of Nephritis.*—Phenolsulphonephthalein elimination varies during the course of the illness (nephritis), a fact well established and one which we have frequently observed. Our most striking example of this is Case 4 in Table 5, in which the phenolsulphonephthalein rose from 17 per cent. to 70 per cent. in five weeks, and in which there was no marked evidence of cardiac disease. The patient's improvement paralleled this rise. We freely concede that a rise as marked as this in so short a time cannot be an index of the actual degree of change in renal tissue, but that it is rather an illustration of the fluctuation in functional capacity during the course of the illness. Thus again, if the phenolsulphonephthalein test is repeated at intervals, its value from the point of view of prognosis is evident. We believe that too much emphasis should not be laid on one phenolsulphonephthalein elimination, and in the differentiation of nephritis from chronic passive congestion, it would seem that a series of both phenolsulphonephthalein and nitrogen tests should be carried out in order to reach any definite conclusions.

3. *Hyperpermeability.*—In the past year, Pepper and Austin[10] have called attention to the existence of cases of nephritis in which the functional capacity of the kidney is normal or even above normal. Baetjer[11] has described such cases and considers that there may be a stage in nephritis when hyperpermeability exists at least to phenolsulphonephthalein and some other substances. We have also noted a few cases, but so far the opportunity for serial studies of them has not been presented. It may be that this so-called hyperpermeability is merely an illustration of the possible existence of damaged kidneys with normal functional capacity, at least for some substances. Cases of this type are usually accompanied by chlorid retention.

In our series of pure nephritis of the chronic interstitial type, several interesting facts may be noted (see Table 4). Nearly every case showed retention of nitrogen, decreased phenolsulphonephthalein elimination and high blood-pressure, while the blood-sugar was slightly

8. Farr, C. B., and Austin, J. H.: Jour. Exper. Med., 1913, xviii, 228.

9. Rowntree, L. G., Fitz, R., and Geraghty, J. T.: The Effects of Experimental Chronic Passive Congestion on Renal Function, THE ARCHIVES INT. MED., 1913, xi, 121.

10. Pepper and Austin: Am. Jour. Med. Sc., 1913, cxlv, 254.

11. Baetjer, Walter A.: Superpermeability in Nephritis, THE ARCHIVES INT. MED., 1913, xi, 593.

TABLE 5.—Result of the Study of a Series of Cases of Chronic Parenchymatous Nephritis

	Case	Diagnosis	Age	Sex	Blood Nitrogen Mg. per 100 c.c. of Blood	Blood Sugar Gm. 100 c.c. of Blood	Phthalein Elimination % in 2 Hrs.	Blood Pressure	Eye-Grounds	Edema	Liver	Albumin	Casts	Sp. Gr.
1.	A. S.	Chronic parenchymatous nephritis	22	♀	....	0.095	27	146/90	.....	++	—	++	++	1.013
2.	W. M.	Chronic parenchymatous nephritis; myocardial weakness	24	♂	33	0.072	20	98/65	Related retinal veins	++	—	++	++	1.028
3.	A. K.	Chronic parenchymatous nephritis	25	♀	74	.....	7	170/130	Normal.....	++	—	++	++	1.019
4.	F. A.	Chronic nephritis.....	24	♀	36	.....	17	115/70	Normal.....	+	—	+	+	1.031
5.	S. G.*	Chronic parenchymatous nephritis	20	♀	81	.....	5	145/110	.....	++	—	++	++	1.020
6.	J.McV.	Chronic parenchymatous nephritis	47	♂	145	0.087	0	140/80	.....	+	4 cm.	++	++	1.012

* At necropsy the kidneys were found to be secondarily contracted.

above normal in six of the fourteen cases studied. It should be noted that nine of these fifteen patients ranged from 26 to 43 years of age, and that the prognosis was grave in most instances.

Less striking results were obtained in a series of cardiorenal cases as will be seen in Table 3. One case gave evidence of nitrogen retention while the phenolsulphonephthalein varied from 8 per cent. to 45 per cent. The blood pressure was high in three cases, as was the blood sugar.

The series of cases of chronic parenchymatous nephritis shown in Table 5 is too short to permit of definite conclusions.

III. THE RELATION OF BLOOD-SUGAR, NITROGEN RETENTION, PHENOLSULPHONEPHTHALEIN ELIMINATION AND HIGH BLOOD PRESSURE

The question of hyperglycemia in high-pressure nephritis is of considerable theoretical interest. Since Neubauer[12] first called attention to this, several workers have confirmed his findings while a few have failed to do so. Thus the present status of blood-sugar concentration in nephritis may be regarded as one of the many points at issue and for that reason is included in these studies. The blood-sugar was determined by the micro method of Bang[13] in which a small amount of blood is required for each test. The blood is obtained by finger puncture, which insures simplicity and the elimination of unnecessary discomfort to the patient. All food was withheld from the patient for at least six hours before the blood was withdrawn. Normal figures by this method lie between 0.06 and 0.1 per cent.

In a former publication, one of us (Hopkins[14]) reported on a study of the blood-sugar in twenty-eight cases of nephritis. Briefly stated, the conclusions to be drawn from that work and the cases here presented are as follows:

A slight hyperglycemia occurs in many high-pressure nephritics and frequently in those with low phenolsulphonephthalein elimination (Table 4). There is no relation between the height of the blood pressure and the degree of hyperglycemia. In most nephritics without high pressure, the blood-sugar is normal. Edema and hepatic congestion do not seem to influence the concentration of blood-sugar (Tables 3 and 4).

Of the eight cases in this series which showed a retention of over 40 mg. of nitrogen, four gave an elevation in blood-sugar. This con-

12. Neubauer: Biochem. Ztschr., 1910, xxv, 284.
13. Bang, I.: Der Blutzucker, Wiesbaden, 1913.
14. Hopkins, A. H.: Am. Jour. Med. Sc., 1915, cxlix, 254.

firms the recent work of Borchardt and Bennigson,[15] who also found nitrogen retention a frequent accompaniment of hyperglycemia.

Of the eight cases in which two or three estimations of blood-sugar were made after the various periods of protein feeding, no constant changes were noted.

Alimentary hyperglycemia was pronounced in three out of four cases in which 100 gm. of glucose were fed by mouth and serial tests of blood-sugar made each half hour for several hours.

CONCLUSIONS

1. Protein feeding in nephritis has a direct influence on the retention of nitrogen in the blood. This is most pronounced in the pure chronic interstitial type with hypertension.

2. The estimation of retention by blood analysis is of definite clinical value from the point of view of therapy, and though this series is too limited to permit of definite conclusions with regard to its prognostic value, our findings so far confirm those of other workers who advocate its usefulness in this field.

3. Chronic passive congestion does not cause an increase of waste nitrogenous products in the blood.

4. In the presence of nitrogen retention, the phenolsulphonephthalein output is usually low and the blood pressure frequently high.

5. Chronic passive congestion may greatly impair the phenolsulphonephthalein output. Variation in the elimination of this dye may also be noted in different stages of nephritis, and in cases with "hyperpermeability."

6. To be of value, the nitrogen retention and phenolsulphonephthalein tests should be repeated at intervals, the value of the former being increased when combined with clinical observations of the patient, diet, etc.

7. A slight hyperglycemia occurs in many high-pressure nephritics and frequently in those with retention of nitrogen and impaired phenolsulphonephthalein elimination.

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15. Borchardt, L., and Bennigson, W.: München. Med. Wchnschr., October, 1913, p. 2275.

A STUDY OF GENERAL AND LOCALIZED EFFECTS OF INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER AND CASEIN IN CASES OF HUMAN CANCER*

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I. INTRODUCTION

In several brief communications[1] we published previously our observations on the effect of intravenous injection of colloidal copper in patients suffering from cancer. We also referred to experiments in which we used solutions of casein. We limited ourselves on those occasions to a brief report of some of our conclusions and referred to our future more detailed publication for a discussion of various results and problems of which we could not treat in our preliminary notes. In the following more complete report we shall especially analyze the relation between various sets of general and local effects of the injection of colloidal copper and casein, and the effect of these substances on the tumors. We shall compare the actions of solutions of colloidal copper with those of casein, and the effect of these substances in patients and in animals inoculated with carcinoma.

Our investigations were the outcome of preceding studies on the action of various sets of substances on animal tumors.[2] We wish here only to refer to a few of our results. We found that various sets of substances, as colloidal metals, certain protein substances and herudin, cause an inhibition or retardation, and in some cases a retrogression, of a certain number of tumors. Through a combination of several substances the effect of a single substance could be much increased. The efficacy of these substances depended especially on the age of the tumors, very young tumors being much more resistant to an inhibiting effect. Of special interest seemed to us the proof that repeated injections of these substances call forth in the injected animals processes of reaction against the injected substance.

These reactions have a double origin, being dependent on changes taking place (1) in the organism of the injected animal, and (2) in

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1. Interstate Med. Jour., 1912, xix, No. 12; 1913, xx, Nos. 1 and 5; Jour. Am. Med. Assn., 1913, lx, 1857.

2. Loeb, Leo, and Fleisher, M. S.: Jour. Am. Med. Assn., 1913, lx, 1857; Fleisher, M. S., and Loeb, Leo: Jour. Exper. Med., 1914, xx, No. 5.

the tumor cells themselves. Thus an immunity of double origin becomes established. The immunity dependent on changes in the tumor cells can be transmitted to successive generations of tumor cells. The immunity thus established tends to prevent the continued effect of the various substances and to make it transitory. The immunity is a specific one; animals and tumors immunized against colloidal copper are immune against colloidal copper, but not against herudin and vice versa.[3]

We had intended to limit our work entirely to animal tumors, being doubtful as to whether animal experiments had advanced sufficiently to permit an extension to the field of human cancer, and it was only at the urgent request of physicians that we undertook our work on patients. While in the course of this work we observed marked improvement in the case of some patients, we stated from the beginning that our work was of an entirely experimental character, and we warned against its use in general practice, and very soon afterward we expressed the opinion that even in the most favorable cases a cure could not be expected through this kind of treatment.

While we thus rated the significance of these experiments from the point of view of direct applicability in the treatment of cancer as not very high, we believe that from the point of view of theoretical interest our observations make a more detailed publication advisable.

2. METHOD OF PREPARATION OF THE SOLUTION OF COLLOIDAL COPPER AND OF CASEIN AND TECHNIC OF INJECTION

For the preparation of colloidal copper we employed Bredig's method, at first, however, making use of an alternating current. Later we used a pulsating direct current obtained by means of a mercury arc rectifier. This passes through twenty-three large lamps of 32-candle power and five small lamps of 16-candle power; the wires terminate in copper electrodes 4 mm. in diameter. These are inserted into a beaker containing 1,500 to 2,000 c.c. of water, twice distilled. The water is first boiled to expel air and used after it has cooled. We used a current of 60 volts and from 16 to 18 ampères. The two electrodes are first brought into contact with each other and then gradually separated so that a spark is drawn out. When the passing of the spark stops, it is necessary to touch the wires again, separating them afterward gradually. This must be repeated again and again. We find it very convenient to attach one wire to an electric bell which keeps oscillating and drawing out sparks continuously. It is best to steam the beakers before using them the first time.

3. The possibility of an immunity against the action of the injected substances acquired through a relatively limited number of injections had been foreseen at an early stage of our work, and determined to a great extent the plan of our experiments. The same possibility we had in mind when we undertook our experiments on human cases and I expressed repeatedly in the beginning of our work the opinion that processes of immunization might prevent a continued efficiency of substances even in those cases which at first seemed to be beneficially influenced; I warned, on the basis of these considerations, against drawing definite conclusions as to the effect of these substances.—*Loeb.*

The copper wires must be cleaned each time with sandpaper before they are ready for use.

Preparation of Various Casein Solutions.—We used different casein preparations, purified as well as non-purified preparations. Into some casein solutions sulphur was introduced, with a view of possibly increasing the efficiency of the preparation. The effects of the various solutions were, in the main, due to the presence of the casein. Solutions prepared with commercial (impure) casein showed approximately the same effects as solutions prepared with purified casein. Addition of flowers of sulphur did not essentially modify the character of the solution. Solutions, however, into which sulphur had been introduced in the form of hydrogen sulphid (Solution 4 and Solutions 4, 16 and 13) were often more poisonous; it is probable that in such cases small quantities of hydrogen sulphid were left in the solution and caused some of the complications which were occasionally observed. The majority of the solutions contained about 1 to 1⅔ per cent. casein.

Technic of Injection.—The technic used in giving intravenous injections of colloidal copper and casein is about the same as that used for injecting salvarsan, except that in the case of colloidal copper and casein it is unnecessary to use normal salt solution either in the beginning or at the end of the injection. A No. 24 Burroughs-Wellcome needle was generally used in our work. We used a pressure apparatus[4] which eliminated all waste of time and enabled the operator to inject as many as twenty-three patients in six hours, two patients being injected at the same time. This apparatus consisted of a reservoir containing the solution to be injected, two dosage containers and a drum for compressed air. The amount of pressure was regulated by a mercury manometer. The fluid in the dosage containers was kept at a constant temperature by an electric stove regulated by a thermostat, which kept the temperature constant within one-fifteenth of a degree. With this apparatus we were able to keep temperature and pressure constant. The pressure we used depended on the way the patient stood the injection, on the size of the veins and on the amount of fluid to be injected, and was regulated accordingly.

3. EFFECT OF THE INJECTIONS OF COLLOIDAL COPPER AND OF CASEIN ON THE VEINS

It is of practical as well as theoretical interest to analyze the effect of the injections of casein and colloidal copper on the walls of the veins with which the injected fluid came into contact after injection.

We consider especially here the pathological changes taking place in the injected veins. The following facts concerning these changes may prove of interest:

1. Injections of casein solutions were tolerated by almost all patients without any resulting changes in the veins. In two cases, however, even the casein had an injurious effect on the veins; both of these cases were in old men, in whom also the colloidal copper had a very marked effect on the veins. In contradistinction to casein, the injection of colloidal copper caused some changes — sometimes very slight and transitory, sometimes very marked and permanent — in the majority of patients. We may therefore conclude that colloidal copper,

4. This apparatus was devised by Dr. W. O. Sweek and made by F. F. Dietz.

and probably also other colloidal metals, cause, in contact with the wall of the veins, pathological changes.

2. In general we can say that the more intimate the contact of the colloidal particles of metal with the wall of the vein, the more marked were the changes.

3. The frequency with which a vein could in the same area be injected with the colloidal copper differed very much in different individuals. In general we can state that frequent repetition of the injections, therefore of the action of colloidal copper, leads to changes, even in cases in which a single injection is without apparent effect. The time required for an affected vein to enable it to return again to its approximately normal condition differed in the case of different individuals.

We may assume that in every case some changes take place in the wall of the vein as a result of the contact with the colloidal copper. In some cases, however, they are very marked, while in others they are very slight. But even in the latter frequent repetition of the injections at a time when the vein had not yet resumed its normal condition leads to a summation of the pathological changes.

4. The changes themselves consist evidently in an injury to the endothelial cells, which makes the latter more permeable to fluid constituents of the blood. Fluid parts of the blood are therefore liable to infiltrate the vessel-wall and the neighboring tissue and make the vein hard and swollen. It is also probable that some of the colloidal particles of copper in some cases enter and irritate the surrounding tissue and then cause a dilatation of the vasa vasorum, thus producing redness of the area surrounding the vessel-wall. Occasionally, the permeability of the vessel-wall may become so markedly increased that edema of a part of the injected extremity follows. Colloidal copper acts, therefore, in this case similarly to certain substances which are supposed to cause, after intravenous injection, edema as a result of injury of the endothelium (as for instance arsenic preparations).

5. It is of great interest that the reaction of the vascular endothelium to injurious influences seems to depend on a sensitiveness variable in different individuals. Even if we allow for differences in the size of the veins, in the rapidity of the flow of the solution in the vessels, in age and general condition of health of the person, there remains usually a factor which points to individual differences. On the whole the veins of strong men are usually more resistant to the injurious effect of the colloidal copper than the veins of emaciated and weak patients; but we found strong men with large veins whose veins proved very sensitive toward the contact with colloidal copper, and, while weak and emaciated women have usually less resistant veins

than strong young women, some old and emaciated patients had resistant veins. In addition, it is probable that a kind of work leading to marked development of the muscles of the arms tends to make the veins more resistant. Two persons whose veins had been most resistant to the action of colloidal copper had both been blacksmiths.

4. GENERAL EFFECTS OF THE INJECTIONS OF COLLOIDAL COPPER AND CASEIN

I. QUANTITIES INJECTED

We started usually with relatively small doses of colloidal copper and of casein and gradually increased the quantities injected, using the general reactions following the injection as an indicator of the rate at which the dose could be increased. The first dose was usually 100 or 150 c.c. of colloidal copper and in the majority of cases it was gradually raised to 400 c.c.; in some cases much larger doses were injected. The time when the dose of 400 c.c. was reached varied in different cases. If the dose was rapidly advanced it could be reached at the time of the fifth injection; in other cases it was reached between the eighth and twelfth injections. The number of injections given in different cases varied in the majority of cases between twenty-five and seventy-three. In some cases only a total of from thirteen to sixteen injections was given. Usually four or five, in one case three or four, injections were given each week.

In most cases in which casein was used the injections followed a preceding series of injections of colloidal copper; but between these casein injections there was usually interspersed a smaller or larger number of injections of colloidal copper; sometimes the series of colloidal copper injections was directly followed by a casein series, and only in the later period of the casein injections were injections of colloidal copper again interspersed among the casein injections. In some cases the initial series of copper injections consisted of more than twenty-five, in other cases of only five injections; the number of copper injections interspersed with those of casein also varied in different cases. In one case there was first given a series of casein injections and later some copper injections were given alternatingly with the casein injections. The amount of casein given in each injection varied much in different cases. Especially, however, in the later period in our work we chose very small initial doses, somewhere between 2 and 5 c.c. In other cases, especially in the earlier period, as much as from 11 to 25 c.c. were chosen as the initial doses, and in some cases even larger initial doses had been given. While some persons could stand these latter quantities comparatively well, in others an extremely strong reaction followed. Gradually in the course of

treatment the doses were increased, in some cases to a maximum of 25 c.c., in others to 50 c.c.; in still others to 90 c.c., and in one patient as much as 155 c.c. were given in one injection. This same patient also received twice at the same injection 200 c.c. colloidal copper immediately followed by 50 c.c. of casein. The number of casein injections given to the individual patients varied very much. Some patients received as many as 48, 46, 36, 32 and 31 injections, others received only between 15 and 21, and still others only a few injections. In most cases two or three injections were given in the course of a week; occasionally there were intervals up to nineteen days between two injections, and in some patients there were, during a certain period, injections given on successive days.

II. THE EFFECT OF INJECTIONS OF COLLOIDAL COPPER ON THE TEMPERATURE CURVE

Intravenous injections of colloidal copper were usually followed by a rise in temperature. This rise began within the first hour and reached its maximum several hours after the injection. In some cases in which a large quantity of the solution had been injected, the maximum rise was reached from five to seven hours after the injection; the temperature usually became normal again on the day of the injection; but on several occasions the temperature was still abnormal on the day following an injection, without a new injection having been given. Thus in the case of a strong man, following the twenty-third injection the temperature rose on the day of the injection to 100 F., and on the following day the temperature was still 99. In this case no complications (as, for instance, an infection) were present which could have explained the rise on the second day. In other cases there was, however, especially in the later stages of the disease, sometimes an infectious process present as a complication which in itself caused a rise in temperature, and to which the rise in temperature caused by the injection was added. In such cases we found a rise in temperature even on days on which no injection had been given.

An analysis of the various cases shows the following factors to be of importance in determining the extent in the rise of temperature observed:

1. The quantity of fluid injected. On the whole we can say that the larger the quantity injected the greater the rise.

2. This factor is, however, complicated by a second factor which, during the period of the later injections, tends to counteract the gradual rise in temperature which should be expected in accordance with the gradual increase in the doses; namely, an immunity which is gradually established as the result of the injections; we shall consider this factor

separately later on. The gradual production of an immunity during the course of the injections makes it necessary to compare in the different cases the effect of the first injections on the temperature. If we do this we notice then that

3. There are individual differences in different patients as far as the rise in temperature is concerned. In some cases the temperature after the first few injections rose hardly at all or not higher than a little above 99 F., and only rarely to 100. This effect we found especially, but not exclusively, in relatively strong persons; in a few rather old and not very strong patients the general reactions were also relatively slight. In a considerable number of cases the rise varied approximately between 99 and 100 F. This class includes a number of weak as well as of strong persons. In a third class, not quite so numerous as the others, the rise varied between 100.5 and 102. This class included mostly weak persons. We find, therefore, as the third factor, individual characteristics, among which the physical strength of a patient seems to be of great importance.

4. In regard to some accidental factors we cannot speak with the same degree of certainty. It seems, however, that some variations in the temperature of the injected fluid (too low a temperature causing higher fever) variations in the size and number of colloidal particles in a volume unit of fluid and perhaps the rapidity of injection had, in some cases, some influence on the degree of fever. We also noticed that if on two successive days the same amount of solution was given, there was occasionally a more marked rise on the second day. We have in such cases possibly to deal with a summation of effects, which, however, cannot consist in a summation of the fever curves, the temperature being usually normal on the day following an injection; but it may consist in a summation of changes somewhere in the body indirectly connected with the rise in temperature. Bacteriological examination of the solutions of colloidal copper proved them to be sterile. The rise in temperature following the injections can therefore not have been due to admixture of bacteria.

III. IMMUNITY ACQUIRED AGAINST THE EFFECT OF COLLOIDAL COPPER ON THE TEMPERATURE

The rise in temperature which followed the injections of colloidal copper became generally less, the larger the number of injections given; this applies to all classes of persons, as well to those in whom the reaction had at first been very marked, as also to those with a reaction of medium strength in the beginning, and to those in whom from the beginning the reaction had been weak. While in the first

two classes the acquired immunity could be easily demonstrated, inasmuch as notwithstanding the larger doses given at later periods the rise in temperature became less, in the last class the establishment of an immunity could be assumed on the strength of the fact that the larger doses given later did not cause a more marked, or even caused a somewhat weaker, reaction than the first smaller doses. In no case was the immunity absolute. There were usually some injections which caused, again, a more marked rise in temperature. In some cases in which at first the reaction had been very marked, it was almost entirely absent in the later periods, while in other cases the difference between the first and later reactions, although present, was not so marked; in these cases the transition from the not immunized to the immunized state was more gradual. In a few cases no definite immunity could be shown to exist. While in some cases this was due to the appearance of complicating processes tending in themselves to raise the temperature, in a few exceptional cases no immunity was apparently produced. In some cases partial immunity became noticeable as early as after the fourth or fifth injection; in others it required from ten to twelve; in still others from fifteen to sixteen injections, before the immunity became marked. After the first sixteen injections the immunity became usually especially marked.

The immunity produced against the general effects of colloidal copper is not specific. It can also be produced through preliminary injections of solutions of casein which on their part cause a marked rise in temperature. We found that in patients in whom, after a series of injections of colloidal copper, a series of injections of casein was given, and in whom after a number of casein injections again a large dose of colloidal copper was injected, the injection of colloidal copper was either followed by no fever reaction at all or by a much slighter reaction than those observed previous to the injections of casein. It appears even probable that many conditions giving rise to a transitory elevation of temperature may thereby lessen the general effects of colloidal copper. In such cases we may have to deal with a lessened excitability of certain nervous mechanisms as a result of previous stimulations.

IV. SOME OTHER EFFECTS OF INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER

Besides the rise in temperature, the most common effect following the injections of colloidal copper was a chill; in most cases beginning about thirty minutes (twenty to sixty minutes in individual cases) after the injection. It lasted usually about half an hour. The presence and intensity of the chill depended, in the same individual, on the

height in the rise of the temperature following the injection. There was a correspondence in the same individual between the severity of the chill and the temperature curve. There was, however, a great difference between different individuals in the liability of a chill to follow the injection. In one patient, a strong man, in whom the temperature showed only slight rises after the injections, there was usually a marked chill present; also at times when the rise in temperature was almost absent. In another patient, an old man, in whom also the rise in temperature was usually slight, a chill was only once observed, viz., after the twenty-fourth injection, when the temperature rose to 100. In typical cases a slight chill seemed to correspond to a rise in temperature to about 101, while a severe chill followed a rise to 102 or higher. In other persons, however, there was a slight chill when the temperature went up to 100, and a severe chill when the temperature went up to 101 or higher; this was the case, for instance, in a girl 16 years old. There were occasionally some other symptoms present; but in most cases they were only exceptionally noticed and found only on occasions when the temperature rose somewhat higher than usual. Such isolated occurrences were: an attack of dizziness, perspiration and symptoms of syncope, pain in head and back, abdominal cramps and vomiting. Other symptoms were on several occasions observed in an old man of strong build. Here the injections were followed by weakness, irregular pulse and vomiting. In an otherwise strong young girl the injections were regularly followed by headache and pain in the arms. When the temperature remained below 100 there was usually no chill, but slight headache and pain in one or both arms were observed.

V. THE EFFECT OF INJECTIONS OF CASEIN ON THE TEMPERATURE CURVE

During the first period the temperature following an intravenous injection of casein was higher than after the copper injection during the corresponding period. This holds good even in cases in which small doses (from 2 to 4 c.c. of the solution) were used during the first injections. In the majority of cases the maximal temperature after the first three or four injections varied between 101 and 104. In some cases it was still higher; in some resistant persons, especially persons of strong build, it did not reach 101. The fever curve after these injections had a steeper course than after injections of colloidal copper, at least in those cases in which large quantities of colloidal copper were injected; the maximum temperature was usually reached earlier than

after injections of colloidal copper, viz., between one and one-half and three hours after the injection; after five or six hours the temperature became usually normal or almost normal again. In some cases, however, in which with the first injections relatively large doses were given, or in which the patient was very sensitive to the casein, the temperature remained high even for considerably longer than a day. In a patient, e. g., in whom, after the first injection the temperature rose on the first day to 105.4, the temperature returned to normal only on the twelfth day after the injection. There seemed to be an individual difference in different individuals, as to the time required in which, after about the same maximum had been reached within a few hours, the temperature returns to the normal point. We must assume that in those cases in which the temperature remains high during a long period, unchanged or only slightly changed casein is circulating in the blood, while in those cases in which smaller doses were given or otherwise the body was normally able to split or eliminate the casein more rapidly, the temperature becomes more rapidly normal. We see accordingly that a long-continued rise in temperature is especially noticeable following one of the first three injections, while later, when a certain immunity has been reached, the return to the normal point is usually more rapid, although the doses given may be much higher than at first. In one person, in whom the temperature remained high during several days, and in whom we gave special attention to this point, the temperature during the afternoon was found to be from 0.2 to 0.6 higher than in the morning.

On the whole the same factors which determined the rise in temperature after injections of colloidal copper are also of importance in the case of casein. The immunity acquired in the course of these injections we shall discuss separately. The size of the doses given determines to a great extent the rise of the temperature. But there remain, besides, individual factors. If we compare several persons who receive in the first injection approximately the same doses, the severity of the reaction is not the same. Thus in one person in whom the injections of colloidal copper caused only very little rise in temperature, casein solutions caused also relatively slight changes in temperature. Here also some strongly built patients seem to be more resistant than weaker persons. Larger initial doses which one patient tolerates with only moderately severe reaction, may cause in another person reactions of a very great severity. If 2 c.c. were given as the initial dose and during the first three or four injections the dose was not increased more than 1 or 2 c.c. each time, only relatively slight or moderately severe reactions were observed.

VI. IMMUNITY ACQUIRED AGAINST THE EFFECTS OF CASEIN ON THE TEMPERATURE

Just as after injections of colloidal copper, an immunity against the effects of casein was produced through repeated injections. In the typical cases we can distinguish three periods in the process of immunization. The first definite signs of immunity became noticeable at the time of the fourth injection about eight days after the beginning of the injections. Then there followed an intermediate period lasting from the fourth to the twelfth or twenty-second injection, during which, notwithstanding the larger doses of casein, the temperature was 1° or 2° lower than in the beginning. This period was followed by a third period comprising the later injections in which, notwithstanding the still higher doses given, the rise in temperature was still more reduced, and in some cases not rarely remained normal after the injections, while occasionally there was a slight rise to 99 or 100, which in a few cases might have been greater. In other cases, however, in which the doses were increased more rapidly, the early onset of the immunity after the first three injections was not so clear. In a strong man, for instance, immunity became clear only after the first twenty injections. Notwithstanding the higher doses given, the temperature was now, on the average, less than after the former injections. In a strong girl 16 years old in whom the fever reaction following the injection was usually very marked, a definite immunity was established only after about thirty-six injections, three months after the beginning of the administration of casein. Immunity becomes established not only in strong, but also in weak persons in whom metastases are present in internal organs at the time of the treatment. In our cases we had of course to deal with the complication consisting in the gradual increase in the doses of casein given. It was therefore possible that in a certain case the immunity existed at a time when the temperature reaction did not decrease in the course of the successive injections, but in such cases the immunity became apparent through the lack of increase in fever in successive injections, notwithstanding the increase in the doses given; the immunity established was in no case absolute, but only partial.

In some cases there was an interval varying between ten and nineteen days between two successive injections. It was of interest to determine whether the injections following the interval would be accompanied by signs of an anaphylactic reaction. While on two occasions it can be definitely stated that such a reaction did not occur, the reaction being not more marked after the injection following the interval than after the preceding injection, on two other occasions the injection following the interval caused relatively severe symptoms.

In those cases in which an anaphylactic reaction can be definitely excluded, we may assume that the quantity of casein given in the course of the preceding injections had been too great to make possible the establishment of anaphylaxis within a relatively short interval of time.

While as we saw, previous injections of casein cause a marked decrease in the general effects following the injections of colloidal copper, the converse condition does not hold good: Preliminary injections of colloidal copper do not protect against the general effects of casein. In this connection we must remember that injections of casein caused very much more marked general reactions than colloidal copper.

If we compare the curve of immunization produced through injections of colloidal copper with the curve resulting from injections of casein, we see on the whole a definite parallelism as to the time when the immunization first becomes apparent and when it becomes more marked.

VII. OTHER EFFECTS FOLLOWING INTRAVENOUS INJECTIONS OF CASEIN SOLUTIONS

Other symptoms besides temperature were more severe after casein than after colloidal copper injections. A chill beginning from thirty to forty-five minutes after the injection and lasting about half an hour was a very common symptom after use of casein as well as of colloidal copper. In the same individual there was on the whole a parallelism between the severity of the chill and the height of the rise in temperature following the injection; frequently a temperature below 101 F. was preceded by a relatively slight, a temperature of 102 or more by a severe, chill. But in the same individual the correspondence between height of rise in temperature and severity of chill was not complete. We find here again a similar difference between individuals as we found in the case of colloidal copper. Some persons were inclined to have a chill after injection of colloidal copper as well as of casein, even in the case of only a slight rise in temperature; in other persons after administration of copper, as well as of casein, a higher temperature was required than in others to produce a chill. When there was a marked rise in temperature, perspiration was not infrequently observed, and after the maximum of the fever had been reached, pain in the region of the stomach and vomiting occurred in a number of cases. These latter symptoms followed much more frequently injections of casein than of colloidal copper. It seems probable that the injection of casein causes contraction of the stomach. A very common symptom after injections of casein was pain in the back, it started often before the injection was finished. This symptom appeared more frequently

in some patients than in others. In some severe cases there was pain over all parts of the body, but sometimes especially localized around the tumor. Thus in a patient with a lesion in the right humerus the arm was affected; in others the face, if the lesion was in the face. In a patient with metastases in the liver, after an injection of a relatively large dose of casein, severe pain in the liver region appeared. In some cases pain around the seat of the lesion was present even if the rise in temperature was very slight. In a few cases this localized pain, appearing about one hour after an injection, was the most persistent symptom next to the rise in temperature. After large doses followed by marked general effects, pain around the tumor may be present one or several days after the injection. In a few cases injections of casein were followed by cardiac and respiratory disturbances: cyanosis, weak irregular pulse and rapid, shallow respiration; in such cases the temperature was usually high, for instance 104.6 in one case. While such attacks were, on the whole, exceptional occurrences, in one or two patients irregular pulse following the injections was a more frequent symptom. It is possible that some heart lesion existed in such patients.

There remain a few exceptional symptoms to be mentioned, viz., herpes labialis, which followed the injection of casein in two cases on occasions when a marked rise in temperature was present. In one patient the twenty-first injection was followed by an erythematous eruption of the skin. On the whole, those casein preparations which caused a more marked rise in temperature caused also more severe other symptoms. With increasing immunity the other symptoms gradually disappeared simultaneously with the fever. In a few cases one of the first three injections was, as mentioned above, followed by very severe symptoms. In these cases, too large doses had been given.[5] It concerned four patients who received the injection at about the same time. The following case may be cited in detail:

Case 1 (No. 3614).—Multiple carcinoma of face and neck. The first injection of 15 c.c. casein was followed by slight symptoms. At the time of the second injection almost 30 c.c. were given. During the injection there was severe pain in the back. For a period of one-half hour there was, every five minutes, a convulsion lasting two or three minutes; the face was red, breathing irregular, pulse rapid. Thirty minutes after the injection there was a severe chill lasting from twenty-five to thirty minutes, followed by a rise in temperature to 106 F., reached five and one-half hours after the injection; delirium and anuria were present, and lasted twenty-four hours. The following twelve days the patient was unable to eat, he lost weight and felt weak. After two weeks he began again to gain in weight and was normal at the end of six weeks. We shall have occasion later to refer to the effects of these injections on the tumor.

5. This was an accidental happening during an unavoidable absence of one of us.

5. EFFECTS OF INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER AND OF CASEIN ON THE BLOOD

I. EFFECT OF THE INJECTIONS OF COLLOIDAL COPPER ON THE NUMBER OF ERYTHROCYTES

We can divide the patients in four categories:

1. In some patients there was a decrease in the number of erythrocytes caused by the injections. This decrease was, however, not very great. Thus, in one well-built patient the number of erythrocytes diminished in the course of ten injections from 5,100,000 to 4,400,000. This decrease is relatively slight. In some cases it is confined to the first period of injections, and in the course of the later injections the number may again increase. In other cases there is a decrease also during the later injections, but after completion of the series of injections a recovery takes place.

2. In some patients in whom anemia was present from the beginning, the anemia progressed during the course of injections, but the decrease in erythrocytes was not more marked than could be expected as a result of the disease. These were patients in whom there were large suppurating or putrid, ulcerated surfaces.

3. In some other cases there was no noticeable decrease, and this applied mostly to less advanced cases, but it was also found in a patient who had at the beginning of the injections 2,100,000, and after a series of fifteen injections 2,200,000 erythrocytes.

4. In one case we found a distinct increase during the course of injections. This was a patient with a carcinoma affecting the orbital cavity and its environment. At the beginning there were 3,700,000, one and one-half months later 4,200,000 and two and one-half months later 4,900,000; nine days after the last (seventy-third) injection, more than three months after the beginning, 5,200,000; three and one-half months after the last injection 6,420,000; six and one-half months after the last injection 4,300,000 erythrocytes. This was the case of a strong man who received very large quantities of the solution at each injection. The maximum was 1,200 c.c.

In some cases we made a count directly before an injection as well as a few hours later. In such cases we found usually a very slight decrease in the number of erythrocytes after the injections.

We may therefore conclude that after the injections of colloidal copper a certain number of erythrocytes are destroyed; that in some cases the reparatory changes which take place suffice to replace the lost red blood corpuscles. Such reparatory processes may occur even in very anemic persons in whom a destruction of erythrocytes took place as the result of other injurious influences, which latter loss the blood-

forming organs were not able to repair. In some cases the reparatory processes are not quite strong enough to keep the number of erythrocytes at the normal level. In such cases the reparatory processes may, however, after cessation of the injections, be strong enough to replace the lost erythrocytes.

II. EFFECTS OF INTRAVENOUS INJECTIONS OF CASEIN ON THE NUMBER OF ERYTHROCYTES

Injections of casein did not usually produce any noticeable decrease in the number of erythrocytes. While possibly in some cases a severe reaction following casein injections may have caused a slight decrease, there was usually no marked difference in the number of erythrocytes at the beginning and at the end of the casein injections. In one case there was even a gain during the period of immunity against the general effects of casein injections. In other cases an increase began to take place after the course of injections had been completed.

In cases in which the disease itself leads to an increasing destruction of erythrocytes, injections of casein cannot prevent the decrease. Intravenous injections of casein have therefore no marked influence on the number of erythrocytes; they neither diminish them very markedly nor do they prevent a decrease produced by other conditions.

III. EFFECT OF THE INTRAVENOUS INJECTIONS OF SOLUTIONS OF COLLOIDAL COPPER AND OF CASEIN ON THE LEUKOCYTES

A complete study of the effect of these solutions on the leukocytes, including a detailed determination of the number of the various leukocytes following injections in each patient, at different periods of the treatment, could not be carried out. In a few cases, however, the leukocytes were studied at different times following an injection. In most cases only one examination was made following an injection and only after certain injections. We may, however, state that a leukocytosis often follows injections of colloidal copper as well as of casein, and that the leukocytosis following injections of casein is usually more marked than the leukocytosis following the injections of colloidal copper. This corresponds with the higher fever which usually follows injections of casein. The maximum of the leukocytosis seems to be reached somewhere between two and five hours after the injections; eight hours after the injections the number of leukocytes is often again normal. In some cases, however, when the general reactions following the injections of casein have been very severe, and fever lasts longer than twenty-four hours, the leukocyte count may still be high twenty-four hours after the injection. Even many injections of either casein or colloidal copper did not produce a complete immunity against the

effect of these substances as far as the effect on the leukocytes is concerned.

The increase in leukocytes was in the main due to an increase in the number of neutrophil polynuclear leukocytes. It is possible that at the same time there existed also an absolute increase in the number of lymphocytes. In some cases in which there existed a relative increase in the lymphocytes, injections of casein produced only a very slight, if any, increase in the total number of leukocytes, but principally a change in the proportion of different kinds of leukocytes. Thus, in the repeatedly mentioned case of a 16-year-old girl there was, three and one-half months after the beginning of the injections, preceding an injection of casein, 9,800 leukocytes. Of these there were 48 per cent. polynuclear neutrophils, and from 50 to 52 per cent. lymphocytes. Three hours after the injection of casein the number of leukocytes had only slightly increased, namely, to 11,000, but the polynuclears had increased to 74 per cent. and the lymphocytes had decreased 50 per cent., namely, to 25 per cent.

IV. A RELATIVE INCREASE IN THE NUMBER OF LYMPHOCYTES PRODUCED THROUGH LONG-CONTINUED INJECTIONS OF EITHER COLLOIDAL COPPER OR CASEIN

The changes in the number of leukocytes mentioned above represent merely transitory changes. It is now of special interest that a large number of injections of colloidal copper or casein, given through a considerable period of time, have, in addition, an influence on the relative number of the various leukocytes, and this influence persists over a long period of time. While the transitory effect consists in an absolute increase in the number of polynuclear neutrophils, the long-continued effect consists in the opposite change, namely, a relative increase in lymphocytes, especially of the small lymphocytes, and a relative decrease of the polynuclear neutrophils. We have observed these changes in all those cases in which the blood examinations were made at intervals through relatively long periods of time. The change became usually distinct about two or two and one-half months after the beginning of the treatment, reached a maximum approximately from three to six or eight months after the beginning and then commenced slowly to decline. This condition lasted, therefore, much longer than the period of injections. It is observed in the following cases:

CASE 2 (No. 3641).—White man, aged 34; multiple carcinoma of the skin. The beginning of the change was noticed somewhat more than two months after the commencement of the treatment and during the period of casein injections. While previously the number of polynuclears had been above 77 per cent., and of lymphocytes 20 per cent., or less, somewhat more than sixty days

after the beginning of the treatment there were 67 per cent. polynuclear neutrophil leukocytes, 27 per cent. small, and 6 per cent. large lymphocytes. About five months after the beginning of the injections of colloidal copper, and three and one-half months after the beginning of the injections of casein, there were 48 per cent. polynuclear leukocytes, 48 per cent. small and 4 per cent. large lymphocytes; the number of leukocytes was increased to 10,800. For the next two or three months the count remained approximately the same, although the total number of leukocytes returned to normal. This change was still present, but perhaps slightly less marked eight and one-half months after the beginning of the treatment and almost two months after the last injection. At that time there were present at two counts made at two days' intervals: polynuclears varying between 48 per cent. and 60 per cent., small lymphocytes varying between 32 per cent. and 48 per cent.; 3 per cent. large lymphocytes, transitional leukocytes varying between 1 and 3 per cent. and eosinophils varying between 2 and 4 per cent. At a count made fourteen and one-half months after the last injection (Aug. 31, 1914) examination of the blood showed the following condition:

Erythrocytes	4,720,000
White blood cells	15,600
Polynuclear neutrophil leukocytes	56 per cent.
Large and small lymphocytes	41 per cent.
Large mononuclear cells	1 per cent.
Eosinophils	2 per cent.

We see, therefore, that this change is not of a transitory character, but persists for a long period of time.

Case 3 (No. 1436).—Woman, aged 69; carcinoma of face, affecting the ear. Two months after the beginning of the injection there were 68 per cent. polynuclear neutrophil leukocytes, 30 per cent. lymphocytes and 2 per cent eosinophils present. Two and one-half months after the beginning of the treatment there were 57 per cent. polynuclears and 5 per cent. eosinophils. Three months and nine days after beginning of the treatment there were 57 per cent. polynuclears, 40 per cent. lymphocytes and 2 per cent. eosinophils. Five months after the beginning and thirty-nine days after the end of the treatment there were 48 per cent. polynuclears, 49 per cent. lymphocytes and 3 per cent. eosinophils. One month later the polynuclears had decreased to 45 per cent. and the lymphocytes had increased to 48 per cent.; there were 4 per cent. eosinophils. Nine months after the beginning of the treatment and five months after the completion of the treatment, the lymphocytes had again decreased to 40 per cent., the polynuclears had increased to 52 per cent., and the eosinophils to 2 per cent. Twelve or thirteen months after the beginning and eight or nine months after the completion of the treatment, there was a further rise in polynuclears, whose number varied between 58 per cent. and 68 per cent.; there were between 31 per cent. and 41 per cent. lymphocytes (about 16 per cent. of which were large lymphocytes). There were also 1 per cent. eosinophils. Similar observations which do not need to be given in detail were made in the following cases:

Case 4 (No. 1476).—Man, aged 59. Carcinoma of the cheek.

Case 5 (No. 1504).—Man, aged 56. Carcinoma of the eyelids extending to the eye.

Case 6 (No. 1502).—Man, aged 57. Carcinoma affecting the skin in the neighborhood of the eye.

Case 7.—R. M., girl, aged 16. Swelling in the humerus of the right arm, diagnosed as sarcoma.

In Cases 3 (1436) and 6 (1502) we can attribute the change to the effect of colloidal copper. In Case 6 (1502) no casein had been given. In Case 7 only a few injections of colloidal copper had been given,

and the changes were in all probability due to casein. In the other cases a larger number of injections of both casein and colloidal copper had been given. This relative increase in lymphocytes is at certain times accompanied by an increase in the total number of leukocytes; at other times the latter is absent. We see, furthermore, that old and young, strong and weak persons, can show this change. We have to distinguish such cases from others in which already before the beginning of the treatment a relative lymphocytosis is present.

In some cases it seems that the first changes in this direction were observed from five to eight weeks after the beginning of the treatment; but inasmuch as no continued examinations of the blood were made in these cases, no definite statements concerning the point can be made.

As to the significance of these changes, it is probable that they represent a reaction of the organism toward all kinds of substances administered during a long period of time which cause a rise in temperature and a transitory increase in polynuclear neutrophil leukocytes. But whether this reaction consists in a mere change in the distribution of the various kinds of leukocytes in the superficial and in the deeper blood vessels, or whether we have to deal with an actual new formation of lymphocytes, cannot be decided with certainty at present, although the latter alternative seems to be more probable. It has been observed by Baeslack[6] that there is an increased lymphocytosis present in cancerous animals during the period of retrogression of a cancer. We can exclude with certainty in our cases any relation of the lymphocytosis to retrogressive changes, which latter took place in some cases long before the onset of the lymphocytosis and in other cases was lacking notwithstanding the lymphocytosis.

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6. Report on meeting of American Association for Cancer Research, 1913, in *Ztschr. f. Krebsforsch.*, 1913, xii, 441. Baeslack mentions also two cases of human cancer (sarcoma of upper jaw and carcinoma of uterus) in which during a period of retrogression there was an increase in lymphocytes. It may be also mentioned that Harlan Shoemaker (*New York Med. Jour.*, 1913, xlviii, 2-18) states that in the treatment of pellagra, after a first period of injections of colloidal copper, in which the polynuclears increase in the period directly following the injections, there is a later period during which the small mononuclear blood cells are increased, and still later the large mononuclear cells appear. This is an interesting observation. We believe, however, that we must distinguish between two phenomena, viz: 1. The temporary increase of polynuclear leukocytes following each injection of colloidal metal. Such a temporary reaction may still be present even at a later period, when the lymphocytes are already relatively and absolutely increased, and this increase in polynuclear leukocytes may superimpose itself on the lymphocytosis. 2. A later lymphocytosis, which in contradistinction to the increase in polynuclear leukocytes is not directly, but only indirectly, caused by the injections; it is a chronic condition lasting for a long period of time, after the injections have been omitted. It is not only produced through colloidal metals, but also through injections of casein and probably other substances causing a temporary increase in polynuclear leukocytes.

6. EFFECTS OF THE INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER AND CASEIN ON THE TUMORS AND THEIR SURROUNDING TISSUES

We may divide the changes which we observed in two classes: (1) in those not directly representing healing processes, but processes more or less common to all tumors, and (2) changes representing a healing process, or the first stage of it, or a process, while not actually connected with healing, bringing some relief to the patient. A sharp line between these two kinds of effects cannot be drawn, and some might be just as appropriately classed with the one as with the other.

I. EFFECTS OF THE INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER AND CASEIN ON THE TUMOR, NOT REPRESENTING HEALING PROCESSES

Besides the general effects which we described above, definite changes take place in the tumors and various tissues surrounding the tumors after the intravenous injections of colloidal copper and casein. *These changes might be characterized as a localized inflammation caused by substances introduced into the circulation at a place distant from the place of injections.* We have to deal with an experimentally produced inflammation. A localized effect is produced through an interference affecting the whole organism. The essential feature of the localized reaction is a hyperemia affecting the tumor and its neighborhood. It may not only affect the immediate neighborhood, but also extend somewhat further into the surrounding parts of the organism, and the extension is generally the greater, the more severe the reaction. For instance, if a lesion is situated at the lower lip and chin, the whole face may become swollen and the conjunctiva injected in the case of a severe reaction; and even the middle ear may show some effect. In open lesions the hyperemia may lead to small hemorrhages, which become noticeable in the form of hemorrhagic scabs over the ulcer or in a blood-stained secretion.

The hyperemia is followed by and is to a great extent the cause of the typical symptoms of inflammation, namely, swelling, redness, increased secretion and sensation of pain or allied sensations. The swelling following the injection can in some cases be seen soon after the injection, and can also be measured in favorable cases. Thus in a patient with a lesion affecting the humerus, the circumference of the arm would increase ½ to 1 inch after an injection. Even after the fourteenth casein injection such an increase could be observed. This swelling takes place sometimes during the period of rise of temperature; it occurs, therefore, before the maximum of temperature has been reached. But it may also be present somewhat later. Thus,

swelling of the neighboring lymph-glands was present four hours after injection and had subsided the following morning. The increase in hyperemia leads in the case of superficial lesions to redness of the surrounding tissue, and sometimes to a bluish purple coloration.

Increased secretion becomes noticeable in ulcerated tumors after the first few injections; for instance, as early as after the second injection. It may follow copper as well as casein injections. Sometimes a clear serous fluid is secreted, but at other times the secreted material may appear purulent or putrid. Infection of the ulcer by organisms is present in such cases. The swelling following the injections is in all probability due to the increased secretion as well as to hyperemia. If the increased transudate cannot be eliminated through an ulcerating surface, it might collect and cause swelling, as, for instance, in a cancerous lymph-gland, or in a lymph-gland not yet itself the seat of a metastasis, but situated in the neighborhood of a tumor.

The hyperemia and increased transudate causes also probably the pain or burning or itching sensation following injections in and around the tumor. These sensations may also radiate into a zone further removed from the tumor. For instance, in a case with a lesion in the right humerus, the pain was often felt not only in the diseased right, but also in the healthy left arm. These sensations are at their height just as the swelling before the maximum temperature has been reached. It may start three quarters of an hour or an hour after injection, and may have subsided within three hours. Local pain may be the most persistent symptom following the injections, more persistent than fever; such was the case, for instance, in the patient with a lesion of the humerus. Pain may be present after an injection of copper as well as of casein. If fever persists for several days after an injection, pain may also be felt for a few days after injection. Even with a slight fever, pain may be severe. Colloidal copper and casein produce essentially the same "inflammatory" reactions, only after casein the reactions were usually more severe; there was more pain, swelling and secretion. The relative intensity of the reactions following colloidal copper and casein varies in different cases. In some cases the reactions — general as well as local — are almost absent after colloidal copper, while they are marked after casein; in other cases they are present after colloidal copper, but stronger after casein.

There exists a definite relation between general and local reactions; in most cases both follow a parallel course. Usually a severe general reaction is accompanied by severe local reactions. For instance, in a certain case in which the general reaction following a certain number of injections was slight, the local reactions were also slight. Then there followed at a later injection a severe general reaction and the

local reaction also was much more marked than previously. In other cases the general reactions following injections of colloidal copper were entirely or almost lacking; in such cases the local reactions were also entirely or almost entirely absent. Furthermore, those preparations of casein which produce the most severe general reactions call forth equally marked local reactions. It may, however, occasionally occur that with relatively slight fever (99.8 F.) at one of the later injections, the local reactions (consisting, for example, in swelling of the face in a patient with a carcinoma of the lower lip) may be very severe. We may therefore conclude that the conditions determining the severity of the local and general reactions are the same; that there may, however, in some cases, in addition to these common conditions, exist some special conditions influencing separately either set of reactions.

We can more or less distinctly distinguish in most cases three periods as far as the character of the local reaction is concerned. In the first period all the inflammatory signs are most pronounced; increased redness and swelling around the tumor may be the first sign; a little later, at a fourth or fifth injection, increased serous discharge may become noticeable. The time relations in the appearance of these different symptoms differs, however, very much; also the duration of the first period, which extends usually from the first to somewhere between the fifth and tenth injection. Then the second period begins, characterized by a decrease in secretion; generally the secretion may become less and less during this period, and the ulcer becomes not infrequently almost dry; the swelling and the redness which existed previous to the treatment also often begins to subside. Quite marked in many cases is the diminution of pain during this stage, sometimes, however, a little earlier, during the first period. The second period is a period of reaction against the first period of more or less intense inflammation. Immediately following the injections there may, however, during the second period still be present local inflammatory reactions, varying in intensity in different cases and at different times in the same case. This second period is also the time when the more definite healing processes set in in cases in which such reactions can be observed. This second period gradually grades quite slowly into the third period of immunity against the local effects of the injections. Just as in the case of the general reactions, the immunity is usually not a complete one in the case of the local reactions; even toward the end of treatment severe local reactions may follow an injection; but gradually the severity becomes less. In some cases these reactions may be absent altogether, especially after a late injection of colloidal copper. Just as in the case of the general reactions, casein immunizes

also against the local effects of colloidal copper, while on the other hand injections of colloidal copper do not immunize against the effects of casein.

These periods, however, cannot be demarcated so sharply in all cases. There was, for instance, a case in which it required seventeen or eighteen injections for the diminution in secretion to become apparent, and this change in secretion was apparently the only difference between the different periods in this case. In another case local reactions appeared as late as the thirty-fourth injection of colloidal copper (throbbing pain around the tumor). In another case the first period extended over the first ten injections, and was therefore rather long.

In these three cases in which there was either no marked demarcation between the different periods, or the first period was of a long duration, the healing effect was also extended over a longer period than in the other cases. In these three cases (Nos. 1436, 1502, 1405), immunization against the effect of colloidal copper evidently took place to a less extent than in other cases.

Just as in the case of the general reactions, we have also in the case of the local reactions to take into consideration the fact that the doses of colloidal copper as well as of casein were in a number of cases gradually much increased as the injections progressed and that therefore a partial immunity may have been masked through the strong effects of large doses. The local reactions which we described were, naturally, mainly observed in the case of superficially situated tumors. But they occur also, as far as we can judge, in internal cancers and in lymph-glands with metastatic growths and internal organs in which metastases have formed.

Such lymph-glands also swell and become painful after injections of colloidal copper or casein during the first period. In one case of a primary carcinoma of the rectum with metastases in the liver, the first injection of 25 c.c. of a solution of casein was followed by pain in the liver region, evidently due to hyperemia in the liver surrounding the tumor. If a lymph-gland with metastic nodules is connected through a fistula with the surface, the increased formation of transudate in the lymph-glands after injections may become apparent. In the second period we may also observe in the glands a diminution in the swelling and secretion. In a case of carcinoma of the esophagus there was less pain in swallowing after the ninth injection of colloidal copper. We may assume that this was due to a decrease in the swelling of the tumor with the onset of the second period. Similar phenomena were observed in a cancer of the breast. The breast as well as the neighboring lymph-glands became painful after injections of colloidal copper. After injections of casein there was also pain present in the axilla and in the

neighboring enlarged glands. Combined with severe general reactions following injections of casein, the pain could be present on days following the day of injection; in this case the fever also extended over a number of days. In the same patient the breast was swollen for one day after another injection of casein had been given. Here, too, we have to assume that increased hyperemia and perhaps increased transudate was the cause of these changes.

In a number of cases of ulcerating cancers we observed that after a relatively small number of injections the discharge from the ulcer, which had previously been putrid, changed its character and became very much less putrid. A possible explanation for this phenomenon is the bactericidal action of the serous transudate which, as we stated, is increased during the first period or perhaps at a somewhat later day; the succeeding increased dryness of the ulcer may also perhaps bring about this result.

While the local reactions may be concerned in the healing process, they are certainly not the only factor determining retrogressive changes in the tumors. The character of the lesion and the general condition of the patient also play a part. Thus we notice that the local reactions may still be present at a time when the healing processes have ceased. There were some other cases in which healing processes took place without marked local reactions or in which healing processes took place at a time when the local reactions had ceased. The opposite also occurs: there may be present marked local reactions without any healing processes being noticeable. On the other hand, we have stated already that in cases in which healing processes are noticeable, they usually set in with the second period. In one case especially a certain connection between local reaction and decrease in the size of the tumor was noticeable. In this case (No. 1405) the thirty-fourth injection of colloidal copper was followed by throbbing pains in the tumor, and in the course of the following few injections the size of the tumor diminished noticeably.

We may therefore conclude that while the local reactions following the injections are in some way directly or indirectly concerned in healing processes taking place in the tumor, these local reactions are not the only factors concerned, but other factors may be of equal or even greater importance for the healing process.

If we now inquire into the mechanism of these local reactions, it appears most probable that the presence of the tumor with the constant development of new vessels produces a special, labile, sensitive condition of the vessels in the tumor as well as in the surrounding tissues. In consequence stimuli, as, for instances, the presence of certain foreign substances, though unable to alter to any noticeable extent the

blood-vessels of normal tissues, have, in contact with these labile vessels, a similar action as the localized injection of certain very irritating substances in the case of normal tissues. In the production of pain the central nervous system is concerned. The radiation of the pain to a symmetrical part of the body (other arm) suggests an irradiation of stimulation within the central nervous system.

It is not probable that such localized reactions are restricted to real tumors, but it is probable that other localized lesions react in a similar manner. This is indicated by one of our cases in which local reactions took place at a time when in all probability the tumor was no longer present, if, indeed, at any time a real tumor had existed in this case.

II. CHANGES IN TUMORS REPRESENTING HEALING PROCESSES

Among the local effects we have already mentioned, some changes induced by the injections which, inasmuch as they brought some relief to the patient, might in a wider sense be classed among the healing processes, as, for instance, decrease in pain, which was marked in a number of cases, decrease in secretion and in putrefaction, diminution in the swelling in the tissues surrounding the tumors or in the tumors themselves. In regard to the latter it is in certain cases difficult to distinguish between the decrease in size due to circulatory changes and a decrease in size due to the destruction of tumor cells, both processes occurring. It will be necessary to consider briefly the effect of the injections of colloidal copper and casein in a few selected cases.[7]

A. NON-KERATINIZING, CYLINDRICAL-CELL CARCINOMAS OF THE SKIN

Case 8 (No. 3614).—In part reported previously. Man, white, aged 34. During first period of the treatment observations were made by Dr. M. F. Engman and incorporated in our previous reports.[8] Multiple carcinoma of the skin on hand, face and neck. Numerous small cancerous ulcers, deeply infiltrating carcinomatous masses, destroying part of the nose, part of the skin in angle of eyes, some parts of lower lip. Lower lids of both eyes eroded. In tissues of left side of face were hard nodes of pea size. Lower lip greatly thickened, hard and everted. Skin rough and scaly. Three elevated plaques on the dorsal side of the hand. Disease started twelve years ago. Roentgen-ray treatment was tried without benefit. Thirty-six injections of colloidal copper; a large number of injections of casein extending over a period of more than four months. The injections of colloidal copper had no or only a very slight effect; our own interpretation of the action of colloidal copper is therefore less favorable than that of the first clinical observation of this case. There was perhaps a slight shrinking in the lesion of the nose; some crusts fell from the lesions, but similar changes had, as we found later, occasionally taken place spontaneously before the treatment was begun. The second injection of casein which had such marked general effects also led to marked local effects on the

7. For the sake of brevity, all other cases, comprising some of patients who were benefited, as well as the majority of those cases in which the results were slight or negative, are omitted.

8. Interstate Med. Jour., 1913, xx, No. 1.

tumor. Twenty-four hours after this injection many lesions appeared as if cauterized; after four days scabs fell from a number of lesions. The lesions of nose and upper lip healed almost entirely with the formation of scar tissue; some of the nodules of the lower lip became softer and disappeared. Some small lesions in the face disappeared; others remained unchanged. The following injections of casein had no marked effect. During the following six

Fig. 1.—Photograph taken before any improvement was noted. (Case 8.)

weeks some of the lesions became softer. At a later period, when immunity had been established, one nodule around the face began to grow again. In a nodule examined microscopically towards the end of the treatment many mitoses were visible. The histogenesis of this tumor has been described elsewhere.[9]

9. Loeb and Sweek: Jour. Med. Research, 1914, xxviii, 235.

The photograph (Fig. 1) shows the condition of the patient at the beginning of the injections of colloidal copper. It shows the large carcinomatous ulcers around the nose and the upper lip. The small lesions in the face, the swelling and ulcers of the lower lip are brought out only indistinctly.

The photograph (Fig. 2) was taken three and one-half months after the beginning of the injections of casein. It shows the healing of the carcinomatous ulcers around the nose and the upper lip. At that time the swelling of the lower lip had become definitely smaller and the ulcerated masses were also somewhat smaller, but had not disappeared. Later this patient was again treated with Roentgen rays without marked benefit.

Fig. 2.—This photograph is not recent. The patient is in better condition than the photograph shows. (Case 8.)

Case 9 (No. 1502).—Man, white, aged 57. Disease began as a small black speck below the eye twenty-five years ago; the lesion grew very slowly. Several plaster treatments led to temporary improvement only. Gradually the eye became involved. Nine years ago Roentgen-ray treatment was given, producing an improvement lasting one year. Eye extirpated. The ulcer grew more rapidly within last five years. There is now a crater-like ulcer involving socket of eye as well as the cheek below. Seventy-three injections of colloidal copper were given within a period of ninety-seven days. Twelve hundred c.c. was the largest single dose given. After the fifth injection an island of new skin began to appear; it increased later to finger-nail size. After seventeen or eighteen

injections the discharge diminished and was less putrid. The ulcerated surface looked healthier. Improvement continued. After the forty-fifth injection new skin extended from the margin of the ulcer deeply into the ulcerated area. The ulcerated area showed a raw surface with numerous patches of what appeared as granulations; some well-marked blood-vessels. During the period between the fiftieth and sixtieth injections the ulcer was again covered with some pus. From the fiftieth injection progress was slow, but the newly formed skin extended somewhat, showing, however, a macerated appearance. After the sixty-first injection there was less discharge, blood-vessels and skin extended somewhat. At the time of the sixty-third injection one Roentgen-ray exposure was given; two days later the general appearance of the ulcer was improved; some more new healthy skin appeared, a few days after the first and second exposures to Roentgen rays. Powder was applied over the ulcer; this led to improvement, diminishing the macerating action of the secretion. During nine days there was no treatment. After sixty-six injections the ulcer was almost entirely covered with skin. Some discharge was still present, originating in the eye-stump, at the seventy-third injection. The ulcer, with the exception of a small area along the side of the nose and at the outside corner of

Fig. 3.—This photograph was taken before treatment of any kind was employed. (Case 9.)

the lower edges of the former ulcer, was covered with new skin. At the end of the treatment most of the ulcer had healed over. There remained still a small ulcerated area one-half as large as a dime at the lower margin of the former ulcer and another one near the eye-stump. It is of interest to note that the progress continued, although the general reactions after the injections were usually slight. In this case we have much longer-continued effect than usual. The two Roentgen-ray exposures may have contributed to the improvement. Of interest also is the healing over, notwithstanding slight local and relatively slight general reactions.

The photograph (Fig. 3) shows the condition of the ulcer before treatment. At no place was the ulcer covered with new skin. Figure 4 shows the condition toward the end of April, after about sixty-three injections and immediately after a second Roentgen-ray exposure. The ulcer looks much cleaner and a bridge of newly formed skin traverses the ulcer.

Figure 5 shows the condition of the patient at the end of the treatment. The ulcerated area is almost entirely covered by skin; only two small places are still uncovered. This condition was still present three months after cessation of treatment. Here also immunity took place. Some small places did not heal over.

Fig. 4.—Patient shown in Figure 3 after about sixty-three injections and immediately after a second Roentgen-ray exposure. (Case 9.)

Illustrating Article by C. B. McClurg, M.D., W. O. Sweek, M.D., H. N. Lyon, M.D., M. S. Fleisher, M.D., and Leo Loeb, M.D.
The Archives of Internal Medicine, June, 1915.

Fig. 5.—Same patient as in Figures 3 and 4, showing the condition at the end of the treatment and also three months afterward. (Case 9.)

CASE 10 (No. 1436).—Woman, aged 69. In part previously reported. One year before the treatment was begun there was present on the bridge of the nose a small pearly growth with some ulceration in the center of the lesion. In the right ear involving the lower third and the auditory meatus, was an extensive destructive ulceration with considerable infiltration and swelling anterior to the mastoid process; the submaxillary lymph-glands were palpable. The lesion on the nose had at that time been present for one year; the lesion on the ear for three years. The patient was given Roentgen-ray treatment every other day until a reaction was produced on nose and ear. When the reaction had subsided, the nose was well and the lesion in the ear improved. She was soon given a second series of Roentgen-ray exposures without showing the same improvement as formerly. The tumor in the ear became larger and in the surrounding skin of the face and part of the scalp there developed eczematoid dermatitis. Staphylococcus vaccines and local antiseptic applications did not improve the dermatitis noticeably. The patient received in all seventy-eight Roentgen-ray treatments and when she entered the hospital in 1912 the tumor of the ear had grown double the size and the lesion on the nose had relapsed to its former condition. There was a discharging ulcerated patch beneath the ear and a tumor mass involving the seventh nerve, producing complete paralysis of the right side of the face. The patient received sixty-two injections of colloidal copper in seventy-eight days; usual dose 400 c.c., occasionally less; later nine injections of casein (2 to 8 c.c.). Corresponding with the onset of the second period healing set in. After the tenth injection of colloidal copper the ulcer appeared slightly shrunken, showing a thin dried scab. After the fourteenth injection the ulcerated area had several islands of new skin, also a line of new skin on the lower border extending upward over the ulcer. The skin around the ulcer appeared very much cleaner. After nineteenth injection the discharge had ceased, except from the auditory canal. The ulcer had healed from below upward, leaving a raw surface about as large as an adult middle finger nail. The skin around the ear was almost normal in appearance; only slight scales were noticeable, where before thick yellow crusted areas existed; clearing up of the eczematoid condition of the skin was simultaneous with healing. During the period from the nineteenth to the twenty-sixth injection the ulcer continued to shrink in size and a healthy crust formed over it. When the crust fell off, the ulcer beneath showed a healthy-looking skin; there existed no redness, edema or infiltrated margin around the ulcer. There was some discharge still from the meatus. After the twentieth injection the glands of the neck also were smaller. After the twenty-fifth injection dermatitis disappeared. Up to about the fortieth injection progress was still present, but slow. New formation of skin progressed, until at the end of the period only a small ulcer remained just below the auditory meatus, connecting with the ulcerated area in the external auditory meatus. During the rest of the colloidal copper injections an ulcer of the size of a split pea remained under the external meatus. After the use of bismuth paste, the skin gradually extended toward the meatus, but no complete healing took place. The principal progress was therefore during the first twenty injections; it depended mainly on the contraction of the skin; but in the second place also on a healing over of new skin. There was some slight but continuous progress for more than two and one-half months. Then there occurred again a breaking down over a small area under the external auditory meatus. On the back of the left hand there was a large scab which would form, come off, and leave a raw, ulcerated surface beneath. After fifteen days' treatment no difference between the two hands was noticeable. The hand remained healed. The lesion on the nose had not disappeared, but was smaller, only a small ridge being left. The skin over the area formerly occupied by the growth under the ear showed some redness and appeared to be thinner than normal skin and had a tendency to form small white scales, which were easily removed. In this case the general

reactions after injections of colloidal copper were slight and cannot be held responsible for healing processes in the tumor.

The casein injections had no effect. During that period the ulcerative process even extended a little beneath and behind the ear for a few weeks and remained from then on stationary. Casein produced much stronger general

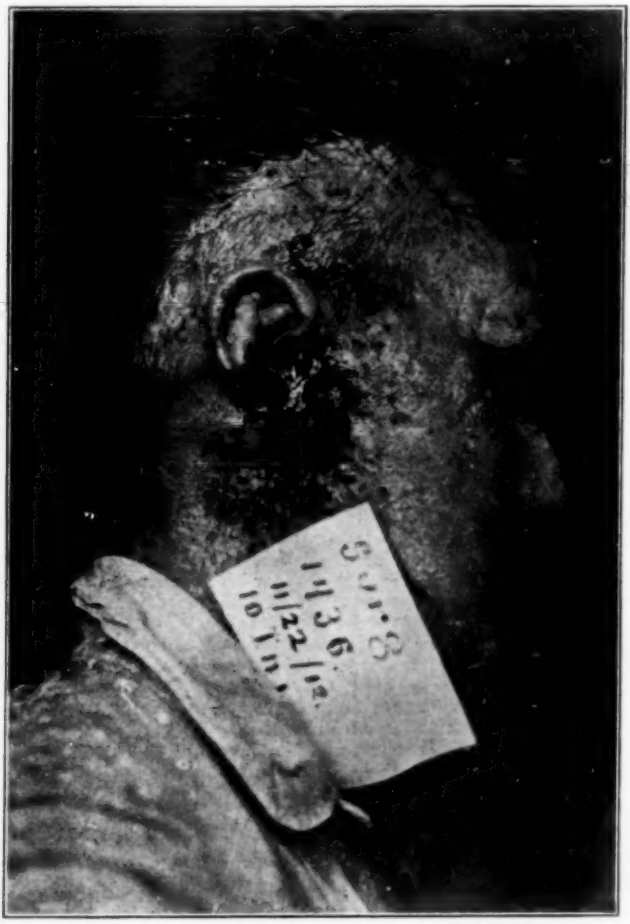

Fig. 6.—Photograph taken before any perceptible change had occurred. The dark spots outside of the ulcerated area are small ulcerated nodules. The date card covers a large mass of glands. This mass is easily palpable and slightly raised above the skin surface, but not sufficiently to show in a photograph. (Case 10.)

reactions than colloidal copper. Microscopic sections through the tumor at the time when it was beginning to progress a little, showed some strands of nonkeratinizing carcinoma with a number of mitoses.

In this case there is a distinct immunization against the effect of colloidal copper noticeable. The main result was obtained in the period between the tenth and twentieth injections. From then on to the sixty-eighth injection the progress was much slower and during the period of casein injections the tumor even extended slightly. The healing remained incomplete. Later Roentgen rays were used without leading to a complete healing.

The first photograph (Fig. 6) was taken before any perceptible change had occurred. The dark spots outside of the ulcerated area represent small ulcerated nodules. The paper showing the date when the picture was taken covers a mass of swollen glands. The second photograph (Fig. 7), which was taken after the injections had been discontinued, shows that the large ulcerated area

Fig. 7.—Photograph of patient shown in Figure 6, taken after the injections were discontinued. The large ulcerated area is now covered by healthy skin. The mass in the neck is gone. The small dark patch in front of the external auditory meatus is a patch that refused to heal, owing to the irritation of the constant discharge from the ear. Examination May 2, 1913, showed that this place had healed and that there was no further progress of the growth. (Case 10.)

seen in the first picture is now covered by healthy skin. At this time also glands in the neck were no longer swollen. The small dark spot in front of the external auditory meatus refused to heal as a result of the discharge from the ear constantly irritating it. This picture also shows the improved condition of the skin around the tumor; the scaly appearance seen in the first picture has disappeared.

Among four cases of so-called basal-cell carcinoma, two were markedly improved, while one showed only a very slight improvement. In the latter case we had to deal with an anemic person with a deep ulcer. In the fourth case colloidal copper was also without noticeable effect, while one injection of casein with marked general effects led to a partial healing. In the latter case we have to deal with an indirect effect of casein. We see, therefore, even in cases representing the same type of cancer, marked variations in the results of the injections.

B. CASES OF SQUAMOUS-CELL CARCINOMA

CASE 11 (No. 1455).—Man, white, aged 46. Three years prior to admission the patient had a sore on the lower lip; about two years later the sore began to spread. Treatment by paste made the condition worse. Now ulcerated area on right side of lower lip beginning at mucocutaneous border; hard everted edges; at lower half edges hang over to extent of 1 cm. Mass hard. Through mucous membrane hard nodules can be felt. Ulcer about 1½ inches in diameter. An enlarged lymph-node under chin. Forty-six injections of colloidal copper (up to 500 c.c.) were given. Following the second injection of colloidal copper there was less pain. Following the seventh injection the edges of the ulcer softened; the ulcer was somewhat smaller. Following the tenth injection it was distinctly smaller; skin began to grow over the ulcer. These changes took place notwithstanding very slight general reactions. Up to the fourteenth injection the ulcer became still smaller. Following the seventeenth injection the nodule under the chin disappeared. After the twentieth injection the mass on the lip became still smaller, softer and could be folded. From then on only very slight changes occurred up to the thirty-first injection. The lip became movable; a little skin grew over the edge of the ulcer. During the casein injections there was no definite progress. Histological character of pieces taken out at an early and a late stage of the treatment was about the same. There was evidently in this case immunity produced after the first twenty injections of colloidal copper.

CASE 12 (No. 1476).—Man, aged 59. Carcinoma of cheek of sixteen years' duration. Cauliflower-like ulcerated carcinoma of left cheek of size of a 5-cent piece covered by yellowish-red scab, raised about 1 cm. above level of cheek. This growth was the center of an indurated area about two inches in diameter which was covered by reddened skin, extending down to but not involving the mucous membrane of the cheek. Could be distinctly felt on inside of mouth. Case declared inoperable on account of size of surrounding indurated area. Thirty-five injections of colloidal copper, eighteen injections of casein. From sixth to fourteenth injection the indurated mass around the tumor began to diminish in size; diminution continued up to the sixteenth injection. From then on there was a stationary condition. From the fourteenth to the seventeenth injection pain in the tumor disappeared. Central tumor not smaller, but easily movable. Casein without effect. Microscopically no change at beginning and end of treatment. Immunity after about fourteen injections; very slight general reactions in this case. After the series of injections the tumor could be apparently easily completely removed through operation.

CASE 13 (No. 1442).—Carcinoma of right cheek affecting lower jaw, extending to angle of jaw and into lower lip. In the lower part of swelling there is a protruding fungus-like ulcerated mass about three-fourths inch in diameter. Thirty-six injections of colloidal copper and twenty-seven injections of casein were given. Following the fourth injection of copper the external mass was somewhat reduced in size; following the tenth injection the tumor masses were smaller; soreness disappeared; patient opened mouth better. Fungus-like

outgrowth on outside of cheek had shriveled considerably and discharges less. After the seventeenth injection some shrinking in oral cavity; mass in mouth became movable; could open mouth much better; external prominence had shrunken. After end of copper treatment (Jan. 15, 1913) no copper found in section of tumor taken out. Four days after first injection of casein which produced marked general reactions, tumor noticeably smaller. Mass within mouth had diminished in size. The mass in the mouth which had been reddish before became grayish-white and appeared necrotic. Part of necrotic material was expectorated. Outer excrescence dried up. No change from further injections. Immunity began after ten injections of colloidal copper and was almost complete after twenty injections. There was also some immunity against general effects of colloidal copper. There was a necrotizing effect of first casein injection on the tumor.

CASE 14 (No. 1405).—Man, aged 74. Formerly reported; irregular ovoid mass apparently attached to periosteum over antrum. Continuous with this mass there is, in the buccal tissue, another swelling that appears on the mucous surface of the cheek as a leukoplakic area, raised about 2 mm. above the surrounding healthy mucosa. On gum and hard palate several small yellow nodules; sixty-two injections of colloidal copper (from 150 to 400 c.c.) From the seventh injection on, less pain in the face. After twelfth injection could open mouth and eat. From the twenty-fourth to the twenty-eighth injection, there were still less pain and further improvement in the general condition. No change in external mass of leukoplakia. During the period from the twenty-eighth to the thirty-sixth injections the external mass diminished steadily in size. At the time of the thirty-second injection the swelling was noticeably smaller. Following the thirty-fourth injection there was marked local reaction and subsequently swelling became markedly smaller . .d had disappeared after the thirty-sixth injection. Up to the forty-sixth injection the tissue concontinued to become softer and more movable, and the mass fixed on the periosteum could no longer be felt. Movements of the mouth were no longer restricted. Leukoplakic area and yellow spots persisted. No further changes took place. Up to the end of treatment microscopic examination of leukoplakic area showed much thickened epithelium with relatively small processes into the deeper tissue and some round-cell infiltration in the connective tissue below. There was a gain in weight during the period of injections. In this case there was no immunity against general reactions, and the main retrogressive change on tumor took place between the thirtieth and forty-sixth injections.

If we summarize briefly the effect of the injections of colloidal copper in cases of squamous-cell carcinoma (including some cases in which the microscopical examination could not be carried out), we find definite retrogressive changes in Cases 1404, 1442 and 1455, changes which could not be explained merely through alteration in blood and lymph circulation. In one case, T., in which the progress had been rapid before the treatment had been begun, at least a standstill followed the injections. In Cases 1499 and 1405 the diminution in the swelling was marked, but it is difficult to determine how much of it was due to alteration in the circulation through the tumor and surrounding tissues as the result of the injections. Such circulatory changes led also to a marked diminution in size in the Cases 1439 and 1298; in Case 1476 they were marked, but concerned the tissues surrounding the tumor proper; they rendered the removal of the tumor through operation possible. In the following cases there was only a

very slight or no retrogressive effect visible, or it was of such a kind that later experience made it doubtful whether the effect was due to the injections or to spontaneous changes: 1430, 1132, 1453, 1458, 1441, 1420, 1504, 1412, 1454. There were, however, some slight effects present in some of these cases; thus Patient 1412 could move the eyelids, close the eye much better and could open his mouth much wider than before. Similar improvement was noted in Patient 1405. There was a decided diminution in pain in the following cases: 1455, 1405, 1458, 1404, 1439, 1412 and 1454. Putrid discharge was diminished in Cases 1458 and 1454. As to the effects of casein, we noticed in a manner similar to Cases 3614 and 1442, and to some extent in Case 1504, that an injection which has a very marked general effect on the patient may cause a part of the tumor to become necrotic, and later on to be cast off; the effect of such an injection does, however, merely affect a certain part and not the whole of the tumor. Otherwise it is doubtful whether injections of casein have any effect on the tumors, although they have more marked general and local inflammatory effects than injections of colloidal copper. There was perhaps a slight effect of casein present in Case 1420, in which the injections of casein preceded those of colloidal copper, and also in Case 1298. Of great interest is the fact that most of the healing changes, or changes leading to the relief of the patient, took place in the course of the first sixteen or twenty injections. Case 1405 was an exception in this respect. The principal changes took place, therefore, in the second period, or in the time directly following it.

In the following case the diagnosis of sarcoma could not be established with certainty:

Case 15.—M., white girl, aged 16. Mother and grandmother of patient had been operated on for cancer. Swelling in right upper arm at junction of upper and middle third, about size of silver dollar, very sensitive to touch; pain especially on motion. Pain was noticed first about three months previously. Diagnosis of sarcoma was made by a well-known surgeon and immediate amputation of arm recommended. Roentgen-ray picture was taken before the injection was begun; she was kept under observation for twelve days; at the end of this period another Roentgen-ray picture showed that the growth had progressed. Circumference of arm at point of disease was 11 inches at the beginning and 11½ inches at the end of the period of twelve days. Six injections of colloidal copper (100 to 400 c.c.) and forty-six injections of casein in 117 days (from 15 to 25 c.c.) were given. After three injections of copper, five days after the beginning of the treatment, the circumference of the diseased arm had decreased ¼ inch. Directly following the first injections of casein there was an increase in the size of the diseased area, which was followed by a decrease. A Roentgen-ray picture five and one-half weeks after the beginning of the treatment (after about twelve injections of casein) showed a standstill in the disease; another Roentgen-ray picture was taken three or four weeks later which showed a new deposit of lime salts in the diseased part; this calcification progressed during the next few weeks; after the thirty-seventh injection about one-third of the area was infiltrated with lime salts. From then

on no or only very slight progress was made till the end of the injection. About three months after the last injection the diseased area was opened through operation. A cavity and necrotic bone were found; microscopically, connective tissue, partly rich in cells, was seen, and some necrotic bone invaded by connective tissue. In this case the diagnosis of sarcoma cannot be made with certainty.

In accordance with our previous observations, we found in a case of carcinoma of the breast that a single general reaction of great intensity following an injection of casein may lead to a partial destruction of tumor tissue. Injections of colloidal copper, in cases of cancer of the breast, led only to some diminution in the size of lymph-glands approximately coincident with the beginning of the second period. We treated three cases of carcinoma of the uterus; two of these were very advanced in very cachectic patients; one was less advanced in a relatively robust woman.

CASE 16 (No. 369).—Negro, woman, aged 30. Examinations by Dr. F. J. Taussig. Patient hysterectomized for carcinoma of uterus about four years preceding the injections. Recurrence. A mass the size of an orange, irregular in outline, palpable, was found in the right iliac region; a similar mass about one-half the size of an orange in the mid-pelvic region; about nineteen injections of colloidal copper (150 to 400 c.c.) were given.

After two days tumor on right side the same; in center a little smaller. After fifteen days right tumor smaller, tumor in center had continued to shrink and had become flatter. After twenty-one days pain had disappeared; there was very slight sensitiveness on deep pressure. No change in consistency. The right tumor continued to get smaller up to the end of treatment; the gland in the center was at that time hardly palpable. After discontinuation of treatment the disease began again to progress. There was no doubt in this case concerning the beneficial effect of the injections, which produced a considerable reduction in the size of the tumor and diminution in pain.

In a non-cachectic patient colloidal copper improved the condition of the patient markedly, causing a noticeable reduction in the size of the tumor. In this as well as in the one of the two cachectic patients, colloidal copper diminished pain markedly, while in the third cachectic patient neither tumor nor pain was influenced. We may furthermore conclude that the injections are capable of influencing, also, tumors other than those of the skin or external mucous membranes.

Some decrease in the size of the tumors was observed in a case of cancer of the thyroid. We leave it open in this case as to how much of this decrease was caused through circulatory changes.

7. CONCLUSIONS

I. SUMMARY OF EFFECTS OF COLLOIDAL COPPER AND CASEIN ON THE HEALING PROCESSES

1. Intravenous injections of colloidal copper have a definite effect in a certain number of tumors, while in the case of others they are without any noticeable effect. It is at present only to a limited extent possible to analyze the factors responsible for this variability in the

results. In a preliminary manner we may conclude that: A. The effect of the injections is not limited to a special kind of cancer. Definite results have been obtained in the smaller basal-cell as well as in squamous-cell carcinoma and in carcinoma of the uterus. The most marked results were, however, obtained with the least virulent, most chronic cases, namely, the smaller basal-cell carcinoma. B. Those patients in whom definite results were obtained were relatively vigorous persons. In cachectic patients and in those with internal metastases, no results were obtained, and in some cases it was observed that following an intermittent disease which weakened the patient very much, injections which had previously had some effect, became indifferent. C. While these factors seem to be of importance, other variable factors seems to play a part, and it is therefore impossible to predict in a given case whether or not a definite result will be obtained.

2. While in some tumors the measurable reduction in size, the shrinking of the ulcerated area, leaves no doubt about the definite effect of the injections on the tumor, there are a number of cases in which a noticeable shrinking of the tumor takes place, but in which the character of the tumors and the rapid effect of the injections suggest that the diminution in size is mainly due to an effect on the circulatory conditions in the tumor, as for instance, in Case 1439. In other cases, as, for instance, 1405 and 1513 (carcinoma of the thyroid), it is doubtful how much of the change observed is due to the circulatory changes and how much to an actual decrease in the quantity of tumor tissue. In one formerly rapidly progressing case the growth came to a standstill during the period of injections. In certain cases the injections do not influence to any noticeable extent the tumor itself, but they cause a marked diminution in the swelling of the surrounding tissues (especially in Case 1476). Through this sharp demarcation of the tumor proper a formerly inoperable tumor may become converted into an operable tumor. There was also an effect noticeable in the glands affected by metastases; a diminution in size was observed in a number of cases; again, changes in the circulatory condition may entirely or partially be the cause of this. In a number of cases a marked diminution in the pain, and, in some cases, in the quantity of the putrid discharge, followed the injections. In a considerable number of cases neither objective nor subjective improvement could be obtained.

3. In most cases the improvement began approximately with the onset of the second period (see general description of local reaction). In almost all cases the improvement after a temporary period of progress came to a standstill. The duration of the period of progress in healing varied considerably in different cases. We noticed a similar gradual decrease in the effects of the injections in the cases of the

general reactions and local reactions in the region surrounding the tumor. There was in some cases a parallelism noticeable in the curves indicating the gradual decrease in the reactions of a general character and those affecting the tumor directly. We may interpret this decrease in the effect of the injections on the tumors in two ways: A. Certain parts of the tumor or certain processes in the tumor are much more accessible to the actions of colloidal copper than others. After they have been influenced, other parts or other processes remain inaccessible to the effect of colloidal copper. B. An immunity is gradually obtained, not only against the general reactions, but also against those local reactions which induce healing processes. Inasmuch as we have proved the existence of such an immunity in the case of animal cancers, and have shown it to be of double origin, it becomes very probable that an analogous immunity is also produced in human cases. In addition, the first-named factor may play a certain part. Thus, it comes about that even in the apparently most favorable cases the healing remains incomplete and later even the progress of the carcinomatous growth may be observed. A similar immunity is produced against the general reactions following the injections of colloidal copper.

4. Microscopical examinations of pieces of tumor excised during different periods of the treatment do not indicate a direct destruction of the tumor. This is not conclusive evidence, however, against the occurrence of such a process, inasmuch as one of us has shown previously that also in definitely retrogressing animal tumors mitoses may still be found in tumor cells.[10]

5. While intravenous injections of colloidal copper have a definite effect, causing a partial retrogression in a certain number of cases, ordinary injections of casein preparations were even without effect or were followed by so slight effects that the distinct efficacy which can to a limited extent be ascribed to colloidal copper cannot be attributed to casein. In two cases, however, there were perhaps slight effects visible (1420 and 1298); these were cases in which the injections of casein had not been preceded by a larger number of injections of colloidal copper. We may interpret this lack of efficacy of casein in either of the following two ways: (A) Casein is actually without effect in human cancer, despite the fact that it is efficient, although to a less extent than colloidal copper, in animal tumors. Or (b) the lack of efficiency is only apparent, caused by the fact that in almost all our cases the injections of casein were preceded by injections of colloidal copper, and that through the preceding injections of colloidal copper an immunity had been produced against the action of casein as far as

10. Loeb: Virchow's Arch. f. path. Anat., 1902, clxvii, 187; ibid., 1903, clxxii, 363.

its direct effect on the tumors is concerned. Then it would be necessary to conclude that such an immunity against the direct effects of casein on the tumor could thus be produced, while, as we saw above, preceding injections of colloidal copper are not able to produce an immunity against the effects of casein as far as its general and certain inflammatory local reactions are concerned.

6. While a definite decision between these alternatives cannot be arrived at at present, we may definitely conclude that there is no thorough-going parallelism between the strength of local inflammatory reactions or the severity of the general reactions following the injections of a certain substance and its direct effect on the tumor.

7. In case injections of casein have an unusually marked general effect, causing high fever, extending over several days, combined with other severe symptoms, they may cause a partial destruction of the tumor within the next few days following the injection. This partial destruction may result in a localized process of healing. In no case was more than a partial effect accomplished by these means. This effect is in all probability not to be considered as a specific casein reaction, but it may be that any other substance causing very marked general reactions would have similar effects on the tumors.

8. As far as the general and local inflammatory reactions following the injections are concerned, our investigations have shown, in accordance with what we assumed from the beginning, that the local reactions around the tumor following the intravenous injections of various substances are in no way specific.

9. Some other investigators have made observations which support the conclusions that intravenous injections of colloidal copper, or of related substances, have a definite effect on a certain number of tumors, while others, the majority, are left uninfluenced. Thus Dr. M. J. Gelpi, in the Department of Gynecology at Tulane University, New Orleans, injected several patients with a solution of colloidal copper hydrate.[11] Among them he observed a case of carcinomatous ulcer of the cheek which healed entirely over as the result of the injections; an indurated area, however, remained unchanged.

Furthermore, there have also appeared reports by various observers in different countries, some on cases which show undoubtedly that injections of various colloidal metals have a definite, though, from a practical point of view, only partial, effect on a certain number of tumors. On the majority of tumors no or only a very slight effect could be determined.

11. A preparation of Mulford & Co., Philadelphia. We tested the same preparation in mouse tumors. See our communication in Jour. Exper. Med., 1914, xx, No. 5. The case will be reported by Dr. Gelpi. In that case also a recurrence may have taken place later.

10. We have found some evidence supporting the conclusion that human and animal tumors are affected fundamentally in a similar manner by certain substances introduced into the general circulation. Colloidal copper has on cancer in animals a definite though by no means very strong effect. It has also an effect on a certain number of human cancers. We proved the existence of a process of immunization in the case of animal tumors after repeated injections of various substances and we analyzed its mechanism. While a proof of this immunity cannot be given in the case of human tumors with the same definiteness as in the case of animal tumors, its existence can at least be made very probable, a conclusion of theoretical as well as of practical importance.

II. SUMMARY OF EFFECTS OF INJECTIONS OF COLLOIDAL COPPER AND CASEIN NOT RELATING DIRECTLY TO HEALING PROCESSES

11. Colloidal copper, and probably also other colloidal metals, in contact with the walls of the veins cause pathological changes. Solutions of casein do so only exceptionally. The intensity of these changes depends on all those conditions which favor or inhibit an intimate contact between the colloidal particles and the endothelium of the blood vessels. The colloidal particles of metals produce, probably through injury of the endothelial cells, a greater permeability of the vessel-wall for the fluid constituents of the blood, and cause sometimes a dilatation of the vasa vasorum, leading to inflammation in the neighborhood of the vessels.

12. Immunity against the effects of colloidal copper produced through repeated injections of the solution is one of the factors determining the rise of temperature following the injection. The immunity produced against the effects of colloidal copper on the temperature is not specific; it can be produced through preliminary injections not only of colloidal copper, but also of casein.

13. Under similar conditions very small doses of casein cause a greater rise in temperature than colloidal copper, and the fever curve is steeper after casein. In individual cases the rapidity with which the fever disappears varies very much; it is probable that the duration of fever depends at least partly on the time during which unchanged or only slightly changed casein circulates in the blood, while in later periods, when the organism is in a position to split the casein more rapidly, the temperature returns more rapidly to the normal point.

14. Injections of casein are followed by an immunity against the general effects of casein; this immunity gradually increases with the progress of injections. It appears as early as after the first three or four injections; on the whole, three periods can be distinguished in its

development. Immunity may be established in strong as well as in weak persons, in whom there may be metastases present at the time the injections were given. Intervals of ten or nineteen days may elapse between two succeeding injections of casein without the appearance of definite symptoms of anaphylaxis. While preliminary injections of casein protect against the general effects of colloidal copper, preliminary injections of colloidal copper do not diminish markedly the effects following the injections of casein. There exists a certain parallelism in the curves of immunization following injections of casein and of colloidal copper.

15. Intravenous injections of colloidal copper or casein, if given through a considerable period of time, cause a relative increase in (especially small) lymphocytes and a corresponding decrease in polynuclear neutrophil leukocytes. This change extends over a long period of time and may still be present many months after injections have been suspended.

16. Intravenous injections of colloidal copper and casein cause in and around the tumors changes which might be characterized as a localized experimentally-produced inflammation called forth at a place distinct from the place of injection through substances introduced into the general circulation. Colloidal copper and casein produce essentially the same "inflammatory" reaction, only after casein the reactions are usually more severe.

17. We can in most cases distinguish three periods as far as the character and intensity of the local reaction is concerned. In the first period all the inflammatory signs are most pronounced. The second period is characterized by a marked decrease in inflammatory reactions. In cases in which the injections lead to an improvement in the conditions of the patients, the healing changes usually set in with the second period; the second period represents a reaction against the first period. The third period is the period of more or less marked immunity against the effects of the injections. Just as in the case of the general reactions, so also in the case of the local reactions, an immunity usually becomes established, which in this case likewise is usually not complete. In a similar manner as in the case of the general reactions, casein immunizes also against the local effects of colloidal copper, while, on the other hand, injections of colloidal copper do not immunize against the effects of casein.

While a certain connection between the local reactions and the healing processes seems to exist, the parallelism is not a complete one, probably owing to the interference of other variable factors.

It is possible — and we regard this as entirely tentative — that the reaction against the acute inflammatory changes of the first period, a

reaction which characterizes the second period and which leads to a diminution in the size of the tumor and its neighborhood mainly through circulatory changes, constitute the essential effect of the injections of colloidal copper, and that in some special cases this change is followed by further healing processes, either by a more marked shrinking of the tumor or by a healing over of the carcinomatous ulcer. Whether an actual destruction of tumor tissue takes place directly or indirectly as the result of the injections, can neither be positively asserted nor denied at present.

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RAT-BITE FEVER*

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I. INTRODUCTION

In 1907 my attention was first called by Dr. E. Libman to an observation which he had made on a patient who had been bitten by a rat, and who, two weeks later, had developed an irregular and intermittent fever, accompanied by a diffuse erythema, and terminating in recovery without sequelae. Though no distinct scientific data were taken at the time, the unusual character of the symptoms attracted his attention. Soon afterward, two other somewhat similar occurrences were remarked by medical associates, but no opportunity was afforded for personal observation of these cases.

The appearance of an article by Horder[1] in 1910 describing three cases of irregular fever following the bite of a rat, and the almost simultaneous occurrence in the wards of Mt. Sinai Hospital of an undoubted instance of similar nature, afforded the opportunity of making a complete study and examination of all the data in this case and a careful scrutiny of the literature of the various countries in an attempt to discover the previous recognition of the symptom-complex and to collate all the information obtainable relative to the subject. It soon become evident that a distinct clinical picture following the bite of a rat in a human being had been recognized in the older and the more recent Japanese literature, as well as in the older American literature, and that there were sporadic references to similar occurrences in the medical archives of at least three nations of Europe.

Since 1910 there has been an increasing number of cases reported, particularly in the British literature, while the recent records of our own country, except for the isolated report of Proescher[2] in 1913, remain devoid of a single instance. On the suggestion of Dr. Libman, and with the desire to give further recognition to a disease both interesting and important and well worthy of a closer scrutiny, the following case is reported, together with a careful review of the literature of all countries.

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1. Horder: Quart. Jour. Med., 1910, iii, 121.

2. Proescher: Berl. klin. Wchnschr., 1912, xlix, 841; Internat. Clin., iv, series 21, p. 77.

II. CASE HISTORY

Patient.—A Russian boy, aged 15, was admitted to the first medical service of Mt. Sinai Hospital (service of Dr. J. Rudisch) Dec. 17, 1910, giving the following history: About two and a half weeks prior to admission the patient was bitten on the scalp by a rat. After the bite he complained of nothing but slight pain. The wound seemed to heal without attention. Two weeks later, on account of pain and swelling about the healing wound, he consulted a physician. The latter found an edema and induration on the scalp over an area about the size of a bean. There were some enlarged cervical lymph-nodes on the same side, which had been there for a week, according to the statement of the patient. The physician made a crucial incision over the site of the bite and swabbed the parts with potassium permanganate. Fever developed three days later. The glands in the neck increased in size and the eye-lids became swollen. There was a purplish discoloration of the face and right eye. Vomiting occurred on several occasions during the previous week. When admitted to the hospital the patient was sent to the isolation house for supposed erysipelas originating in the wound.

Physical Examination.—December 18. Patient well nourished; does not look seriously ill. No cyanosis or dyspnea. Temperature, 102.2 F.; pulse, 100.

Skin: Over the entire right cheek, right side of the forehead, right side of the neck, right ear, and over a small area behind the right ear there is a diffuse erythema of which the margin is only moderately well defined. Over the area on the neck are a few large blebs and superficial excoriations (due to the use of local applications).

Nodes: Cervical, axillary and inguinal nodes on both sides are slightly enlarged.

Scalp: Over the right side behind the angle of the jaw there is a group of enlarged lymph-nodes; 3½ inches above the right eye is an open wound discharging a small amount of serum. The wound is surrounded by a slight induration and some edema.

Heart and Lungs: Negative.

Liver: Extends to the free border of the ribs. Upper border of flatness in the fifth intercostal space.

Spleen: Edge distinctly felt one finger below free border; hard and round. Extremities and reflexes normal.

Course.—December 19. Edema and erythema have spread to the other side of the face and eyelids. The temperature has become normal.

December 20. General condition good. Temperature normal. No signs of progress of erythema. Original wound is almost clean.

December 22. Patient discharged, well, the induration about the wound and the erythema having disappeared.

Abstract of Clinical Data.—Temperature: See chart. Pulse: Ranged from 70 to 90 or 100, then 68 to 72. Respiration: Normal. Amounts of Urine: Normal. December 18. Clear; acid; 1.030; trace of albumin; no acetone or indican present; moderate number of hyaline and granular casts and some leukocytes. December 20.—Trace of albumin and many hyaline and granular casts and moderate number of leukocytes and occasional erythrocytes. December 22. Faint trace of albumin; few leukocytes; no casts.

Treatment.—Patient treated symptomatically as an erysipelas case.

Summary.—It will be noted that the patient having been bitten by a rat, the wound promptly healed. After an incubation period of two weeks, edema and erythema occurred about the healed wound. Incision and cauterization of the parts were ineffectual in preventing spreading inflammation. Regional lymph-nodes were early enlarged. Fever appeared shortly after the inflam-

matory signs. After a course of five days, characterized by fever and local inflammation, erythema, adenitis and mild nephritis, the symptoms spontaneously resolved.

The patient was readmitted to the first surgical service of the hospital Dec. 29, 1910, and was transferred to the first medical service Jan. 11, 1911.

Surgical History.—The patient stated that two days before admission (or eight days after resolution of previous symptoms) a small mass developed behind the lobe of the right ear. It was painful and tender. The swelling had steadily increased, and the patient said he was forced to keep his head bent to the right shoulder so as to relieve the pain. He felt feverish and somewhat chilly. He was not hoarse, but swallowing was painful.

Physical Examination.—This revealed no new symptoms. The wound was healed; there was no erythema. The cervical nodes were markedly swollen; other lymph-nodes not enlarged. Lungs and heart negative. Liver not palpable; spleen palpable two fingers below the free border of the ribs, firm and round. Temperature, 102 F.; pulse, 100. The urine showed a severe nephritis to be present.

December 29: Aspiration of nodes with negative results.

December 31: Temperature normal.

(The defervescence marks the end of a second paroxysm characterized by swelling of nodes, fever, chilliness, dysphagia and pain in the wound).

January 3: Urine examination shows a faint trace of albumin and a few epithelial cells and leukocytes.

January 8: Urine examination negative.

January 9: The regional nodes are slightly larger. There is slight tenderness of the sublingual lymph-nodes. Axillary nodes not palpable. During the preceding nine days the temperature has remained normal and the patient has been comfortable.

January 11: Temperature shows another rise, reaching 101.6 F. There is no change in the wound. Behind the ear, extending backward to the trapezius muscle and downward to the anterior border of the sternocleidomastoid muscle is an erythema which is, for the most part, patchy. In places it is confluent, pink in color, slightly elevated, resembling urticarial erythema. A group of enlarged lymph-nodes exists behind the angle of the jaw, extending to the lobe of the ear; the mass is the size of a plum, the nodes are quite tender. There is one small, tender lymph-node in the right axilla. Left axillary nodes just palpable. The spleen is palpable 1½ fingers below the free border of the ribs; the edge is round and firm. The liver is palpable two fingers below the free border of the ribs.

Blood-Counts: January 2.

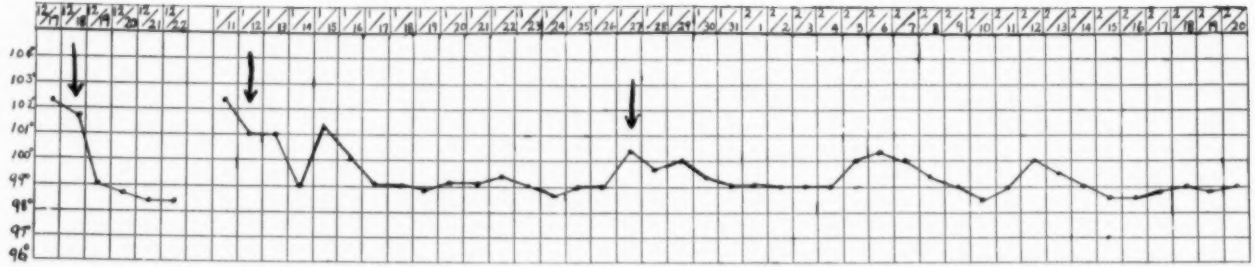
Erythrocytes	5,000,000
Leukocytes	16,000
Polymorphonuclear leukocytes	75 per cent.
Lymphocytes	21 per cent.
Eosinophils	4 per cent.

January 9.

Leukocytes	11,000
Lymphocytes	20 per cent.
Polymorphonuclear leukocytes	80 per cent.

The patient was transferred to the medical service.

Second Medical History.—Examination January 12. The patient is somewhat apathetic. In the right temporal region is the original rat-bite; extending from one-half inch from the median line backward as far as the coronal suture there is an area of slight edema which on pressure is not tender, and which extends down over the posterior half of the right side of face. At the angle of the jaw there is a mass of lymph-nodes about the size of a lemon;



Temperature chart of author's case of rat-bite fever. Arrows mark rises of temperature accompanying successive paroxysms. During the period between December 22 and January 11, the patient was not under observation.

somewhat tender, not attached to the skin; the nodes are somewhat matted together in this region. The submaxillary nodes are enlarged but not tender. There is fulness in the right supraclavicular fossa, and also in outer half of right pectoralis major muscle, this area being tender on deep palpation. In the right axilla the nodes are matted together. Posterior cervical nodes are somewhat enlarged; lymph-nodes elsewhere in body slightly increased in size. There are no changes of any importance in the mouth or throat.

Liver: Palpable two fingers below free border; edge sharp and smooth.

Spleen: Palpable two fingers below free border; edge smooth and hard.

Temperature, 101 F.; pulse, 96.

Urine: Very faint trace of albumin; otherwise negative.

January 13. Spleen broad and palpable one finger below free border. Nodes are larger and more tender.

Blood-Count:

Erythrocytes	4,800,000
Leukocytes	9,000
Polymorphonuclear leukocytes	62 per cent.
Small lymphocytes	17 per cent.
Large lymphocytes	17 per cent.
Large mononuclears	2 per cent.
Eosinophils	2 per cent.

January 17. During the last four days the temperature has been defervescing and the erythema has almost entirely disappeared. Nodes in the submaxillary region are growing progressively larger; otherwise lesions the same as before.

[This paroxysm (the third) occurred after a free interval of ten days. It was characterized by early regional and general lymph adenitis, fever, chilliness, local erythema, enlargement of the spleen and nephritis.]

January 23. Urine shows a very faint trace of albumin; no casts.

February 15. Since the last note the general condition has remained good; patient is up and about. Lymph-nodes still enlarged, not tender; diminishing in size. Erythema disappeared shortly after the end of the last paroxysm.

February 17. Notes on discharge: No edema; no erythema present. Incision (made in removal of lymph-node) behind the ramus of the jaw is healed primarily. Behind the ramus of the jaw there is a lymph-node the size of an almond which is rather firm and quite tender. Surrounding this node there are a number of firm, tender nodes, lobular in form, varying in size from a pea to a hazelnut. Down to the supraclavicular region there is present a large number of lymph-nodes of the same type as those described before, about the size of a pea.

The glands are not matted together, but some of them are connected by strands, apparently of fibrous tissue. Just below the angle of the jaw on the left side there is present a lymph-node about two-thirds the size of an almond, and fairly soft in consistency. In the supraclavicular region on the left side there are no lymph-nodes.

In the left axilla no lymph-nodes are palpable.

In the right axilla two lymph-nodes are felt agglutinated together, fairly soft in consistency, each about the size of a small pea.

In both inguinal regions there are small, fairly soft lymph-nodes about the size of split peas.

In the right recumbent position, splenic dulness begins in the sixth space in the axillary line. Spleen, on deep inspiration, comes down two fingers' breadth below free border. Edge is sharp and hard.

Liver dulness begins in the fourth space in the mammillary line, but is not enlarged downwards.

Lungs and heart are negative. Patient in good condition.

Temperature: For the temperature January 11 to 17, see chart. After January 18 the temperature was practically normal, except for an occasional rise to 100 F.

Treatment.—Purely symptomatic.

(This patient was seen by Dr. Libman a number of times up to March 15, 1911. There had been no further acute attack; the lymph-nodes on the angle of the right jaw were still moderately enlarged and the spleen was still palpable).

Pathological Data.—A blood-culture was made by Dr. Daniel Poll Dec. 17, 1910, when the temperature was 102. Fifteen cubic centimeters of blood were used. The blood was distributed in plain bouillon, glucose-bouillon, agar and glucose-agar. It was incubated partly aerobically and partly anaerobically. No growth in any of the mediums was observed (time of observation six days).

A second blood-culture was made Jan. 9, 1911, when the nodes were enlarging. Fifteen cubic centimeters of blood were used. This was inoculated in ordinary bouillon, ordinary agar, and glucose agar, and grown aerobically, with negative result.

Blood was also inoculated into deep tubes of glucose-agar (according to the Veillon method) and observed for two weeks. Results were entirely negative.

At the same time further examination of the blood was made. Smears were stained with Giemsa, Jenner, Gram stain and India ink. Search, carried out for a number of hours, was negative. Hanging drop made from the fresh blood gave negative results. Examinations by means of the ultramicroscope were also negative. Microscopical examinations of laked blood (method of Fried and Sophian) were negative.

February 4, one of the nodes behind the angle of the jaw was excised. This node was the size of a lima-bean, soft on section, succulent, and of a bluish-gray color, with a thin capsule about it. Smears were made from the node-tissue and were examined fresh, suspended in salt-solution, and by the ultramicroscope. No bacteria or other parasites were found. Smears stained with Giemsa, Jenner stain and India ink also showed no form of parasite. Part of the node was fixed in the usual manner, and stained with the ordinary laboratory stains, as well as according to the Giemsa method of section staining. No parasites were found after careful study of these sections. Histological study of the node showed only hyperplasia and hemorrhage.

Cultures were made from the parenchyma of the node and inoculated on serum-glucose-agar, in glucose-bouillon, on plain agar and on blood-agar, prepared according to the method of Novy and MacNeal (rabbit-blood, one part; agar, two parts). Anaerobic cultures were also made from the node material, blood-agar and serum-glucose-agar being inoculated. These cultures all remained sterile, except for an occasional colony of *Staphylococcus albus*, which was regarded as a contaminating organism.

SYNOPSIS OF CASE

A review of the important features of this case presents the following points of interest:

A young boy was bitten on the scalp by a rat. After an incubation period of two weeks, edema and erythema about the wound occurred. This was soon followed by fever, chilliness, and swelling of the regional lymph-nodes. Incision of the wound did not relieve the symptoms. The patient was admitted to the hospital and treated as a case of erysipelas, on account of the extensive raised edematous erythema which had originated from the wound. Five days after the onset of these symptoms resolution took place and the temperature became normal. Moderate nephritis was present; the spleen was enlarged. This was the end of the first paroxysm.

After a free interval of eight days, swelling of the regional lymph-nodes again took place. Fever, chilliness and dysphagia occurred. There was no erythema. After four days resolution was noted, the spleen and nodes only remaining enlarged. Temperature again became normal.

After a second free interval of ten days the third paroxysm occurred, being characterized again by swelling of lymph-nodes, followed soon by fever, erythema and leukocytosis. Duration of this paroxysm was eight days. Complete resolution of all the symptoms followed, the spleen only remaining enlarged. The urine had become normal.

Throughout the case no marked weakness was noted; emaciation, cachexia and sweating were absent. No nerve symptoms were observed.

Pathological examinations were entirely negative. No parasites were observed.

III. DESCRIPTION OF THE DISEASE[3]

1. *Definition.*—Rat-bite fever (*Rattenbiss-Krankheit*) (*Sudoke*) is a disease incident on the bite of the rat and followed after a variable incubation period by a single paroxysm or by regularly recurring paroxysms of chills, fever and sweats, lasting a few days, and associated with the occurrence of a local or diffuse bluish-red exanthem. The disease is often characterized by marked nervous symptoms. The course of the malady is signalized by progressive emaciation and weakness; the duration is variable, often very prolonged. Fatal cases are not infrequent. The actual cause of the disease remains unknown.

2. *Historical Survey.*—This disease is best known in Japan; the older, and to us inaccessible, Japanese literature is known to present several cases, collected and published by Katsura in 1890. More recently, in 1899, Miyake[4] published a careful study and analysis of about twenty-seven later cases with the additional facts culled from a personal experience of eleven new cases. Miyake stated that in Japan the disease is a fairly well-recognized one, well understood by the medical profession and dreaded by the laity. It is noteworthy that the older American literature presents many cases sporadically observed and published during the last century, almost all occurring during the settler period of this country's growth, and before the introduction of accurate scientific and bacteriological methods of investigation. An occasional reference to this disease is met in the more recent Scotch, Spanish and French literature, though general knowledge or recognition of the clinical picture is never noted. The German literature presents no cases up to recent years. As a well-defined clinical entity it is thus noted that the disease has remained unobserved and undescribed except by the older Japanese physicians. An analysis of the

3. The facts herein presented are collected from fifty-two cases reported in the world's literature up to January, 1914, and the preceding original case.

4. Miyake: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1899, v, 231.

incidence and symptomatology of the disease is based on the full reports of the following cases:

Japanese	24 cases
American	17 (including my case)
French	2 cases
Scotch	1 case
British	7 cases
Italian	1 case

3. *Etiology.*—A. Incidence: The disease seems to have been observed in America, Spain, France and Scotland. Miyake attributes the frequency of its occurrence in Japan to the simplicity of the abodes in that country, the houses being built of wood; the presence of the rat as a parasite is encouraged by this fact. Its existence during the early days of American settler life is similarly explained by the crudeness of the dwelling-places and the constant presence of the disturbing rat. The complete absence of noted cases in the German Empire is surprising.

B. Occupation: Farmers and people leading agricultural lives are most frequently affected; also seamen, on account of the known tendency of rats to inhabit the hold of ships. All classes of society subject to the bite of the rat, however, are subject to the disease.

C. Age: The age of the afflicted person seems to be variable, the injury being the result of accident, and occurring in those whose means of livelihood or wandering spirit brings them into the haunts of the rat. Grown children, particularly boys, and adult men are the commonest victims. The following figures represent the age incidence:

From 1 to 5 years	1 case
From 5 to 15 years	10 cases
From 15 to 35 years	11 cases
From 35 to 55 years	18 cases
After 55 years	7 cases

D. Sex: This, depending on the same circumstances, shows a natural predominance of males (males, 31; females, 20).

E. Previous Illness: There seems to be no relationship between any previous disease and the occurrence of this malady; nor does the constitutional condition of the person bitten seem to affect the development or non-development of the clinical picture after the initial lesion. Miyake, in attempting to explain why only certain instances of rat-bite were followed by the development of the typical symptoms of the disease, while others failed to show any deleterious after-effects, was of the opinion that the constitution of the patient at the time of the bite was the deciding factor. This point has not been borne out by any of the subsequent writers or by an examination of the literature of the earlier cases.

F. The Causative Factor: The disease always follows the bite of a rat. The type of animal causing the initial trauma has not been carefully noted; usually it is described as a "large brown" or a "large black" rat; it is almost always noted as large — that is, adult size and form. The white rat and mice, are not known to cause the picture.

The condition of the animal at the time of the injury is not well understood. Some of the most severe results have followed the wounding of sleeping persons by wandering and apparently peaceful animals; in other cases the wound has been dealt by an infuriated animal, fighting to defend its life. The temper of the rat at the time it inflicts the wound does not seem to play a rôle in the incidence or in the severity of the ensuing illness.

The question whether all rats, or only some rats, are able to inflict the disease is also one of interest. It was claimed that only sick rats were infectious; but this hypothesis must remain for the present undetermined, as no instance of the examination of the animal inflicting the injury is at hand; all the animals have remained at large, uncaptured.

Nor is it claimed that every bite inflicted by a rat on a person is followed by the clinical picture shortly to be described, for instances are known in which the same individual on several different occasions had been bitten without evil consequences, while a subsequent bite has resulted in the establishment of a long febrile course with well-marked symptoms. The determining factors, both as regards patient and as regards the rat, remain for future study to identify.

To illustrate the point that the previous condition neither of the rat nor of the afflicted person is a predisposing factor deciding the severity or non-severity of the disease, the following interesting case is quoted from the literature (see Cases 35 and 36):

Two female children aged, respectively, 12 and 9 years, were bitten by the same rat at the same time. The first child developed the disease in a mild form, lasting only four weeks, and intermittent in character. The second child developed an extremely severe type, the temperature being at first continuous, then intermittent, the course lasting four months, and threatening the life of the sufferer.

G. Location of Wound: The site of the injury was as follows:

Face and head	11
Hand and arm	36
Leg and foot	3
Not noted	2

There is no evidence that the location of the wound determines the severity of the illness to follow. The face and head injuries seem to run a more severe course, the average incubation period for head and

face injuries being eight days, as opposed to fourteen days for extremity wounds. The average duration of the disease resulting from head injuries is sixty days; from extremity injuries, sixty-six days. The eventual prognosis as to life is unaffected by the site of the wound.

As to the actual nature of the injury inflicted, the severe results seem to follow the more superficial injuries; slight scratches in which not even blood is drawn may be followed by a severe clinical course, while deep penetrating wounds may give rise only to the mildest pictures.

It is also difficult to understand why in a case in which a person receives simultaneously several bites from an animal, all except one injury should become quiescent, while the one shows the typical inflammation and induration associated with the recurring paroxysms.

4. *Pathological Anatomy.*—But little is known on this subject. In practically every case the local wound heals without incidence until the occurrence of the paroxysm, when there is noted a painful swelling and indurated, firm edema about the bite-wound. The nature of the disturbance about this point seems to be of an inflammatory character; vesicle formation may occur; frequently ulceration, superficial or deep, is noted. Occasionally a progressive sloughing or necrosis of the tissues is seen, though the latter grave pathological changes are unusual. A secondary and lasting atrophy of the member may follow the resolution of the process. Suppurative inflammation, or distinct phlegmon, is practically unknown. Examination of the regional lymph-nodes, practiced in a few instances, demonstrated only hyperplasia.

Twice only has a necropsy been performed in fatal cases. The results have been briefly summarized by Miyake as an increase of cerebrospinal fluid and congestion of the pial vessels. No further pathological changes are recorded; detailed post-mortem findings are not accessible. The bacteriological and biological studies gathered from the literature will be discussed in a subsequent paragraph.

5. *Symptomatology.*—The clinical picture of a typical case of rat-bite fever is as follows:

A. General Description: The infliction of the wound is followed by an incubation period averaging twelve days. During this time the local lesion usually heals uneventfully and the patient remains unconscious of the fact that he is harboring a pathological process. The first paroxysm is ushered in by a chill or repeated chills, malaise, inability to work; the site of the wound begins to swell, and becomes indurated and bluish-red; the lymphatic vessels stand out inflamed and reddened, and the regional lymph-nodes show early inflammatory enlargement. Within a few hours fever is established, usually from 103 to 105 F.; the pulse becomes rapid and small, the patient much

prostrated. Marked sweating, occurring throughout the paroxysm, marks the remittent drops of temperature. The fever, chills or chilliness and local inflammation continue throughout the duration of the paroxysms. After one or two days, a bluish-red raised exanthem appears on the body, sometimes locally in the vicinity of the wound, sometimes universally. This rash lasts as long as the paroxysm, and disappears with it. Marked nervous symptoms may occur; the reflexes are increased, hyperesthesia or paresthesia is complained of; pareses may appear; dysphagia, muscle pains, etc., may be prominent. The urine frequently shows the presence of a nephritis, varying from mild to very severe. After a variable duration, varying from four to five days, the paroxysm is terminated by profuse sweating.

A free interval now occurs during which the patient is exhausted and suffers from general weakness. He is usually unable to leave his bed or undertake any work. At the end of the free period (from three to five days) the second paroxysm appears, this again being followed by a free interval. This order of alternating paroxysms and periods of release from symptoms continues for a variable period; there may be only one attack, or there may be as many as twenty-six.

The disease usually exhausts its strength as it progresses; the succeeding paroxysms occur at longer intervals, and are maintained for a shorter time, until finally all active symptoms cease. Throughout the course, and long after it, loss of nutrition is marked; cachexia may be severe, convalescence is prolonged and the patient's natural strength returns but slowly.

The fatal cases are severe from the onset; the course is a short and stormy one; nephritis is usually the direct cause of death.

B. Description in Detail: Incubation Period: The duration averages twelve days. In the severer and more prolonged cases, this period is shortened to one, two, three or five days; it may, however, be prolonged, particularly in milder cases, to eighteen, twenty-one or twenty-six days. Thus, the incubation period endured one to five days in eleven cases; six to fifteen days in twenty-seven cases; sixteen to thirty-five days in ten cases; sixty days in one case. The relation of the incubation period to the duration of the illness is shown in the following tabulation:

Incubation Period	Duration of Illness
From 1 to 5 days	111 days
From 6 to 15 days	50 days
From 16 to 35 days	54 days

Thus it is seen that the severer and more prolonged cases have a shorter incubation period; in fact, in two cases the incubation period was a matter of hours. These may be regarded as fulminating cases.

In the older Japanese writings, cases are discussed in which the incubation period was said to have extended over from six months to a year, but the facts in these cases remain open to doubt. The two cases reported of symptoms occurring within a few hours of the infliction of the injury (Cases 16 and 41) both terminated fatally.

The incubation period is usually free of untoward symptoms; the wound heals primarily by first intention in the majority of cases, and the bite is forgotten before the first paroxysm occurs.

Prodromata: These consist usually of swelling and induration occurring about the site of the healed wound. The lymphatics that drain the area stand out prominently, reddened and tender. Associated with a localized bluish induration there is frequently seen a broad area of edema. The regional lymph-nodes are very soon involved, swollen to the size of a bean or hazel-nut, tender and discrete.

The general symptoms are those of a toxemia; there is malaise, headache, pains in the muscles and back, and tenderness along the main nerve trunks. After one or two days of these symptoms the first paroxysm occurs.

Onset: The paroxysm is ushered in by a chill, or chilliness, and a rapid rise of temperature. The temperature may reach 103 or 105 F., remaining practically continuous, with slight remittences, throughout the duration of the active symptoms. The chill may be frequently repeated throughout the course; profuse and drenching sweats are frequent, non-odorous, usually described as "cold sweats." The fever, coming to an end by crisis, is marked by a profound sweat. Occasionally, mild cases are met, described as afebrile. These are uncommon.

The most common type is the intermittent type, in which the fever recurs with every paroxysm and persists throughout its duration. Some of the paroxysms, occurring late in the protracted course of the intermittent type of the disease, may be afebrile, the general symptoms being noted, but fever remaining absent. A continuous type of temperature occurs infrequently. In this variety the disease seems to consist of one prolonged seizure; there are no relapses.

The local changes occurring at the onset have been described above; there are few variations to be noted. Not infrequently in severer forms of the malady a vesicular eruption occurs about the wound. The vesicles may rupture and ulcerate; when this occurs, the ulceration may be progressive and profound; deep sloughing of the edges may be the precursor of a localized gangrenous process, persisting for months and followed by lasting atrophy and disuse of the member. Suppurative inflammation is almost unknown; when it does occur it is always secondary to an open wound which has not received proper attention.

Primary incision of the inflammatory zone occurring locally with each paroxysm, is always futile.

The lymphadenitis is marked, and is, moreover, persistent; the nodes, once swollen, remain so throughout the course of the disease. They partially resolve during the free intervals, only to reassume their inflammatory characteristics just preceding the establishment of each paroxysm.

The Paroxysms: Number: There may be only one paroxysm, short and mild; this is the abortive form of the disease. There may be only one attack, but this may be eminently severe and toxic, and end fatally. There usually are from three to ten repetitions of the seizures; as many as twenty-six have been recorded. As the disease progresses, the paroxysms occur at greater intervals and are less severe in nature. The fever may absent itself; when it does, the toxic symptoms are materially modified and more easily borne.

Duration: This is usually five days; less often only three days; occasionally, and more particularly in that class of case consisting of one paroxysm, up to twenty days. Prolonged cases beginning with paroxysm of five-day type, may show late in the course paroxysms of one-day type. On the other hand, milder cases may show only repeated one-day seizures, with long intervals separating them.

Interval: The interval between attacks averages four days; frequently shorter, rarely longer. An attack occurs always at least once a week; the interval is prolonged as the disease progresses toward a favorable termination.

Nature of the Exanthem: It consists of a few large spots, varying in size from that of a dime to that of the palm of a hand, slightly raised or flat circulate spots. The lesions are bluish-red in color, erythematous rather than urticarial.

Situation: Usually generalized over the body; often, however, occupying only the region in the neighborhood of the wound. Occasionally vesicles or pustules are observed interspersed with the erythematous spots. A distinct urticarial generalized eruption, occurring toward the end of the course, was twice noticed. A purpuric eruption is once referred to.

Gastro-Intestinal Symptoms: The tongue is usually coated and white. Nausea is common with the paroxysms. Constipation is usual; diarrhea not at all infrequent, though usually mild.

Prominence is given in a number of reports to the symptom of dysphagia, coming on early with every recurring paroxysm, completely absent in the interval. It is usually associated with salivation, occasionally with huskiness of the voice, or even aphonia. The dysphagia may be so severe as to resemble rabies, with which rat-bite fever has been confused. The liver and spleen are occasionally enlarged.

Respiratory Symptoms: In prolonged and fatal cases, terminal pneumonia has been noted.

Vascular Symptoms: No reference is made to acute cardiac conditions as symptoms. Chronic endocarditis is once noted as a complicating factor. Myocardial weakness occurs as a result of the severe toxemia. The pulse is usually recorded as rapid and small.

Renal Symptoms: Nephritis was observed nine times in this series of fifty-two cases. It is a severe, often fatal complication; in fact, the most frequent cause of death. The nephritis seems to be of the nature of a glomerular affection of the kidney. The urine shows variable amount of albumin and hyaline and granular casts.

Examination of the Blood: See later under Results of Pathological Examinations.

Nervous Symptoms: The symptoms referable to the peripheral nerves and spinal cord are frequently encountered and form one of the prominent features of the clinical picture. There is an increase in the tendon reflexes; also stiffness about the joints in the affected extremity; paresthesias and hyperesthesias are common. Extremities may show a lasting atrophy after the cessation of active symptoms. Persistent neuralgic pains, referred to the main nerve trunks, have been noted for years after convalescence.

The highest centers seem to be affected during the height of the morbid process. Marked irritability, associated with rigidity of the neck, is common; this may progress to active delirium or give place to stupor or even profound coma. Reference is made once to the occurrence of hemiplegia.

6. *Course and Duration of the Disease.*—The duration varies from a few days to six months, the average being about two months. The following tabulation presents this more precisely:

Duration	No. of Cases
Less than one week	2
From 1 to 4 weeks	10
From 1 to 2 months	3
From 2 to 4 months	6
6 months	2
2½ years	1

In the case cited by Frugoni[5] (Case 52) the course of the illness was protracted for two and one-half years, though there were long intervals of health between the later attacks.

In order to understand the variability in the symptoms and in the progression of this illness, it is necessary to classify the cases on the basis of the duration of the symptoms and the character of the paroxysms. We may thus recognize the following groups:

5. Frugoni: Berl. klin. Wchnschr., 1912, xlix, 253.

A. Afebrile Type: This is a rare form, characterized by the occurrence of subjective symptoms of a mild nature. Neither rash nor nerve symptoms have been observed. The duration is a few days, and the first paroxysm is also the last. These are usually ambulatory cases.

B. Type with Continuous Temperature: There are two subtypes. The first is an abortive form consisting of a single paroxysm, associated with fever and marked subjective symptoms; the entire picture disappears in a few days. The second is a severe, usually fatal, form in which the symptoms are initiated by a severe chill or chills, high temperature and oppressive toxic phenomena. The course is progressive, uninterrupted by free intervals; the local symptoms are marked. Nephritis is early established and the fatal issue may occur within one week of the onset of the symptoms.

C. Type with Intermittent Temperature: This is the common and most frequently recognized type. It has been fully described earlier in the paper. Its duration is about four weeks, but the paroxysms have been observed even after six months. It constitutes over 50 per cent. of the cases. The progressive and marked cachexia and emaciation constitute one of the most prominent points in the course.

D. Miscellaneous Types: Under this heading may be included Case 32, reported by Banker,[6] in which the local symptoms predominate, sloughing and gangrene of the wound being progressive and death resulting from the severity of the nephritis; also Cases 16 and 41, in which the symptoms seem to have been established directly on reception of the injury, or within a few hours. The incubation stage was absent, and the severe toxic subjective phenomena that almost immediately seized the victim culminated in an early death.

7. *Prognosis.*—This is, in general, good. In the series of cases herein cited, fifty-two in number, five (or about 10 per cent.) ended fatally. The majority of cases run a milder or severer intermittent course in which each succeeding paroxysm is weaker than the preceding one, until in time all the symptoms disappear. The loss in strength and weight persists long after the cessation of active symptoms, but it, too, ceases in time. The fatal cases are usually short, violent and stormy in their course; nephritis and marked nerve symptoms early supervene; delirium, stupor and coma attest the severity of the toxic phenomena.

8. *Treatment.*—Until recently it has generally been considered that there is no specific remedy for rat-bite fever. Arsenic in different forms, iron, salicylates, potassium permanganate, have all been used without affecting the course of the disease.

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6. Banker: Am. Pract. and News, 1886, new series, xi, 70.

The prophylactic treatment has been strongly urged by Miyake. He has used early cauterization with phenol (carbolic acid) in all instances of animal bites, and since utilizing this method has not seen the development of the clinical picture.

In 1912 Hata[7] published his series of cases from Japan, in which salvarsan had been given intravenously. The injections were administered in the course of the febrile paroxysms, usually in the presence of fever, from twelve to ninety days after the bite had been inflicted. The result in all the instances was remarkable, the temperature falling immediately to normal; in only one instance was there a febrile reaction. In two of the eight cases reported, an abortive paroxysm followed the injection; this marked the last of the active symptoms. Twice it occurred that after an interval a relapse took place; in one of these cases a second injection of salvarsan resulted in a complete cure.

Thus it is noted that salvarsan, here as in syphilis, seems to exert a specific influence.

9. *Results of Pathological Examinations.* — Blood-cultures and blood-smears have failed to throw any light on the etiological factor or agent of the disease. The local focus has been repeatedly examined for evidence of parasites, but with the exception of the presence of pyogenic bacteria in one case (sloughing ulcer of the extremity) no offending organism has been ascertained. Excised nodes show hyperplasia and congestion. In one case an excised nodule from the hamstring muscles added no information.

Ogata,[8] in his two cases, has described parasitic organisms in the blood, in smears from excised lymph-nodes, and in smears from the local lesion. These organisms are uniformly similar in nature, and are classed by him among the sporozoa. He has observed them to fecundate and produce sporozoites; merozoites also occur. Ogata further reports favorable results with attempted transmission of the disease to animals; his rabbits were easily inoculated, and not only did not survive the disease, but extirpated glands from these animals inoculated in a second group of rabbits caused the establishment of the characteristic symptoms in the latter. Ogata found the organisms in both of his cases. His work has not been confirmed by the more recent observers.

Examinations of the blood during life show a slight anemia early in the course of the disease; later an advanced anemia becomes established. The white blood-corpuscle count, taken between the febrile paroxysms, is not increased; taken at the height of the fever, there is

7. Hata: München. med. Wchnschr., 1912, lix, 854.
8. Ogata: Deutsch. med. Wchnschr., 1908, xxxiv, 1099.

a well-marked leukocytosis varying from 16,000 to 21,500. The relative proportion of polymorphonuclear leukocytes may rise to 87 per cent. An increased proportion of eosinophils may be present, on three different occasions observed to be 8, 11 and 15 per cent.; in another case 5 per cent.

Blood-cultures have failed to throw any definite light on the etiological factor. In addition to the observations of Ogata just mentioned, Middleton[9] (Case 47) reports the finding of a diplococcus once in a blood-smear and culture. Proescher[2] reports the finding of minute bodies in smears of the blood (Case 40).

IV. SUMMARY

What is the nature of the disease? Are we dealing with the results of a living parasite, transmitted from the rat to man by means of a bite, or is this a disease caused by the implantation of a peculiar and highly toxic substance?

In the nature of its course it resembles most clearly relapsing fever, the febris recurrens of the Asiatics and Europeans. The diseases resemble each other in the intermittency of the symptoms; the incubation period in both is variable. In its favorable reaction to salvarsan the disease has a common factor with both syphilis and relapsing fever, but more particularly with the former. The finding of a spirochete as the cause of both these latter diseases suggests this as the etiological factor in this malady. In the prominence of the nervous symptoms and the post-febrile paralyses, rat-bite fever recalls relapsing fever. The one reported post-mortem examination in this disease revealed a serous meningitis, with increase of cerebrospinal fluid. The irregular paraplegias and atrophies recall the tabetic lesions of lues.

Many authors have indicated a belief in one of the species of protozoa as the etiological factor, but with the exception of Ogata, whose work has unfortunately not been confirmed, such parasites have not been observed. Again, the dysphagia, so marked in Case 25, calls to mind rabies, of late again suspected of being a protozoic disease.

Many of the symptoms of this malady might be the result of a powerful toxin elaborated at the site of the wound and transmitted along the regional nerve paths to the central nervous system, in a manner similar to the propagation of the toxin in tetanus. The extension of the toxin to the posterior ganglions might again recall the dysphagia symptoms analogous in rabies. In the light of a case reported by Banker, the possibility of a neuro-toxin, locally created, must be considered. Banker remarks on the permanent atrophy and

9. Middleton: Lancet, London, 1910, i, 1618.

paralysis of the arm only, following on a bite of the hand of the same limb.

To summarize, the point in favor of a spirochete as the causative agent is the similarity of the disease to relapsing fever and syphilis, as regards both the marked nerve symptoms and the apparent curability by salvarsan. In favor of a protozoan cause is the alternation of the paroxysms with afebrile periods, recalling the effects of the malarial plasmodia, though this occurs also in spirochetal diseases.

That the disease is actually caused by living parasites seems strongly upheld by the success of both Proescher and Ogata in inoculating successive generations of guinea-pigs, thus reproducing many of the essential characteristics of the disease.

Appended is a summary of the cases gathered from the literature on which these generalizations have been based.[10]

CASES FROM LITERATURE

JAPANESE CASES

CASE 1 (Irishawa[11]).—Girl, age 7, bitten on the left index-finger; wound healed in three days. After incubation period of eight days local inflammatory reaction, lymphangitis and axillary lymphadenitis. Two days later, fever. Bluish-red exanthem on arm after seven days. Course, irregular fever, marked delirium and stupor at times. Spleen not enlarged. Urine negative. Duration three months. Recovery.

CASE 2 (Miura and Toriyama[12]).—Woman, aged 32, bitten on middle toe of foot; incubation period fifteen days. Intermittent febrile course; paroxysms three days in duration, introduced by chills and characterized by vomiting, muscle pains, headaches, increased reflexes, peripheral pareses, and mild edema; increasing severity, finally collapse and death. Necropsy reported as negative. No details given.

CASE 3 (Miyake[4]).—Woman, aged 43, bitten between thumb and first finger; superficial wound, healing in three days. Incubation period ten days. Chills, fever, sweat; wound becoming red, swollen and painful. Tongue clouded, moist; pulse rapid; temperature 103 F. Edema of arm and cervical region. Thumb much swollen. Over upper extremity bluish-red exanthem from size of five-cent piece to that of palm of hand. Marked lymphangitis and regional lymphadenitis, general muscle tenderness. Temperature intermittent type, paroxysm three days in duration. Course not followed.

CASE 4 (Miyake).—Man, aged 47, middle finger bitten, next day general reddening of finger. Incubation one week; swelling of forearm; fever and chills and associated typical exanthem. Patient markedly prostrated. Tongue coated. Spleen not enlarged. Course not followed.

CASE 5 (Miyake).—Boy, aged 6, slight superficial bite on nose, inflicted during sleep. Incubation period three days. Swelling of wound accompanied

10. In perusing the literature it has not been unusual to meet with instances of the bite of animals other than the rat. The bite of the cat and of the weasel are distinctly described as giving rise to symptoms similar to the disease under discussion; nor are the results of scorpion and spider bites very much dissimilar.

11. Irishawa: Tokyo med. Ztschr., 1897, xi.

12. Miuri and Toriyama: Tokyo med. Ztschr., 1897, xi.

by chills and fever and appearance of exanthem on face. Slight diarrhea. Pulse rapid. Temperature moderate. Glands of neck swollen, plum-sized and tender; nose entirely swollen. General edema of face. Course, good; no return of symptoms.

Case 6 (Miyake).—Man, aged 40, bitten seventy days before on nose. Five to six days later face swollen; fever lasting four days. Slight diarrhea present. Prostrated; marked anxiety. Irregular return of fever. Duration about seventy-eight days.

Case 7 (Miyake).—Man, aged 27, very severe bite on hand. Wound healed uneventfully. Incubation period fifteen days. Paroxysms beginning with repeated severe chills. Fever, malaise and pains in joints; profuse sweating. Swelling of wound; duration of paroxysm not noted. After five days free interval, recurrence. Only at third attack were lymphangitis, lymphadenitis and exanthem noted. Physical examination two months after bite; patient pale, poorly nourished, complained of great pain on movement of right arm. At site of bite dark reddish scar, soft tissues up to elbow swollen, very painful. Exanthem on arm, axilla and neck. Areas of hyperesthesia and increased reflexes. Generally lymph-nodes not enlarged. With the onset of fever, great prostration, oppression, stiffness of neck, headaches. Irregular, intermittent, periodic temperature; interval varying from five to eight days between attacks. After ninth and tenth attacks a general urticaria noted. Result, recovery.

Case 8 (Miyake).—Man, aged 55, superficial bite on forehead, incubation eighteen days. Onset with fever and prostration followed in three days by the appearance of a generalized exanthem. Physical examination seven weeks later; patient poorly nourished, markedly cachectic, scar of bite bluish-red, infiltrated. Face edematous. Diffuse and profuse erythematous exanthem over body. Cervical glands markedly swollen. Paresthesias. After several attacks, appearance of an urticaria. Course, two and a half months. Result, recovery, except for persistent and marked malaise and emaciation.

Case 9 (Miyake).—Man, aged 41, slight bite on finger. Incubation period two days, followed by swelling of finger and appearance of fever; slight general edema over body (old cardiac condition). Urine shows albumin and casts. Blood examination negative.

Nephritis disappeared with the cessation of illness. Course not followed.

Case 10 (Miyake).—Man aged 32, several bites received at same time, arm, cheek and thumb; after twenty-sixth-day interval swelling of arm noted; axillary glands much enlarged. From wound in thumb streptococci and *Staphylococcus aureus* cultivated. Nephritis present. Temperature fell by crisis. Course, intermittent rise of temperature, third paroxysm beginning with subjective symptoms, but only rise of temperature and a few new spots appearing. Result, recovery.

Case 11 (Miyake).—Female, age not noted, penetrating bite of finger. Incubation period three days. Severe paroxysm lasting twenty days. Physical examination six months after bite: Patient poorly nourished, emaciated, wound entirely healing, cervical glands swollen, sternal tenderness and muscle pains persist; persistent general malaise; every attempt at mild physical exercise followed by rise of temperature.

Case 12 (Miyake).—Woman, aged 34; patient bitten previously four times by a rat, without sequelae. Ten days after the last bite on hand, pain in wound, swelling and induration. Attacks last five days; recur after three-day free interval. Patient shows marked cachexia, dark induration of wound, marked diarrhea. Paroxysms initiated by chill and rise of temperature; during the height of fever marked stupor. Temperature falls by crisis. Course one month. (No interference remarked with nursing child.)

CASE 13 (Miyake).—Man, aged 30, finger strongly bitten. Incubation interval eight days. Marked diarrhea. After one month pale, cachectic and sick-looking. General circular exanthem. Blood negative. Course not noted.

CASE 14 (Ogata,[8] Tokio, 1908).—Woman, aged 45, bitten on wrist; incubation ten days followed by chills, fever, pain and redness in wound, and local vesicle formation. Three attacks repeated at three-day intervals. At point of injury, bean-sized ulcer formed, with undermined edge; axillary glands swollen.

CASE 15 (Ogata, Tokio, 1908).—Woman, aged 44, bitten on forehead; profuse bleeding, rapidly increasing edema noted. Edema persistent, forehead swollen, eyes closed, deep necrotic ulcer at site of bite. Ulcer covered by black crust. Thick purulent discharge. Cervical glands enlarged. On thigh one large erythematous spot with two tiny vesicles. These latter vesicles contain thick mucoid serum. Complete pathological studies made of blood, ulcers and extirpated glands in both cases. Author found pictures resembling amebic parasites. (See discussion in article.)

CASE 16 (Nishimura,[13] quoted by Miyake).—Woman, aged 63, bitten on left eyebrow; slight abrasion. Next day cold sweat, palpitation. By afternoon of succeeding day dizziness, tiredness, slight, dull pain in wound. Dyspnea, general paralysis; partial suppression of urine, collapse symptoms. Two and a half days after bite swelling of face. Death in collapse on tenth day.

CASE 17 (Taniguchi, quoted by Hata[7]).—Woman, aged 62, bitten on two successive nights on left eyebrow; ten days later infiltration, reddening, and swelling of entire left face, neck and breast; fever and chill; paroxysm lasted four days; returned at intervals of three to four days. Emaciation, infiltration of wound, localized erythema; enlarged regional lymph-nodes; anorexia, headache, delirium, malaise. During fifty days, eight attacks of three days' duration. On third day of each paroxysm always crisis with sweating. Quinin and arsenic without result. After the eighth attack, case regarded as hopeless. Salvarsan 0.4 gm. injected. Only one attack thereafter and then within four weeks patient was entirely well. Later relapse, lasting for four attacks; no particular treatment.

CASE 18 (Taniguchi, quoted by Hata[7]).—Girl, aged 16; three wounds on nose; seventeen days later chill, fever and pain in wound with swelling of face. Fever continues, then intermittent, with two-day intervals. Emaciation, edema of face, swelling of glands, anorexia, etc. Intervals, from two to three days. Duration three days. At third attack 0.4 gm. salvarsan. One attack of fever without subjective symptoms after injection. Then well.

CASE 19 (Katayama, quoted by Hata[7]).—Woman, aged 29; bitten on right cheek; very soon increasing redness, etc.; swelling of glands, fever, anemia, malaise. Incised two weeks later. Thin pus; salvarsan 0.3 gm. intravenously. Complete local and general recovery almost immediately.

CASE 20 (Katayama, quoted by Hata[7]).—Child, aged 10; left foot bitten. Incubation period fifteen days. Edema, swelling, incision and escape of thick pus. Urticaria, fever; necrosis of wound. Fever becomes remittent. Generalized adenitis. Salvarsan 0.3 gm. Immediate critical fall of temperature and patient thereafter well. Recurrence; further course not followed.

CASE 21 (Shibukama, quoted by Hata[7]).—Woman, aged 79, bitten on left arm. Several weeks later swelling, reddening, etc., which gradually disappeared. First rise of temperature two and a half weeks after bite. Seven attacks in one month. Duration of attacks three to four days. Salvarsan 0.6 gm. Recovery immediate.

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13. Nishimura: Quoted by Miyake, Note 4.

CASE 22 (Sakurane, quoted by Hata[7]).—Woman, aged 37. Left wrist bitten; after ten days, swelling; thirteen days, fever, chill, etc. Salvarsan three weeks after bite, followed by reaction of chill, fever and local pain. Then recovery.

CASE 23 (Shimizu, quoted by Hata[7]).—Girl, aged 2½ years; bitten on right ankle; after one month, swelling, edema, exanthem. Rise of temperature every day. Spleen palpable; localized symptoms greatly exaggerated. Salvarsan 0.09 gm. three months after bite. No symptoms for ten days, then relapse. Salvarsan 0.1 gm. Immediate recovery.

CASE 24 (Yosikawa, quoted by Hata[7]).—Man, aged 22, bitten on finger. Local symptoms marked. Febrile attacks for two months. Then salvarsan 0.4 gm. Rise of temperature to 40.1 C. Immediate fall of temperature. Recovery.

AMERICAN CASES

CASE 25 (Watson,[14] 1840).—Seaman, aged 55, bitten over right eyebrow, while sleeping; incubation period two weeks. Swelling of face, neck, painful induration. Marked dysphagia. No constitutional disturbance. No fever noted. Wound scarified; gradual subsidence of symptoms and inflammation; no recurrence.

CASE 26 (Packard,[15] 1872).—Boy, aged 7, bitten on finger; after two weeks redness and swelling; gland in axilla enlarged; wound incised; no pus found. Three days later appearance of erythema over arms, shoulder and body, marked muscle tenderness, high fever; disappearance in five days; occasional recurrence of rash without constitutional symptoms.

CASE 27 (Earle,[16] 1872).—Man, aged 40, bitten on hand. Wound healed in two days. After nine days local reaction. Tongue coated; erysipelatous condition. After four days return of symptoms, local and general. Glands enlarged; chilliness. Iodin used freely. Second paroxysm, duration five days.

CASE 28 (Reece,[17] 1872).—Man, aged 38, farmer; bitten on finger. Incubation period ten days; local reaction, fever, chilliness, malaise; great pain in finger. Iodin used locally. On the fourteenth day, incision, which was negative except for a little yellow serum. On the seventeenth day, dysphagia, soreness of muscles, mental fear. On the eighteenth day, local necrosis; marked sweating. On the twenty-first day, recurrence, perspiration, enlarged glands. On the twenty-ninth day, abscess in axilla of same side; 2 ounces of pus removed. After six weeks patient not entirely well, nervous and weak, easily exhausted; pustular rash appeared lasting several days; marked muscle pain persists; after six months still unable to do any hard physical work. Dyspnea, palpitation and weakness on exertion.

Author quotes another case of bite on shoulder in sleeping baby; diffuse erythema occurred in a few days. General vesicular rash. Duration five days; recovery.

CASE 29 (Banker,[6] 1886).—Man, aged 20, bitten on forefinger. Incubation five days; generalized pains, localizing in twenty-four hours in finger. At local site a tiny vesicle appeared; general darkening and induration of bite. Marked lymphangitis, chills; temperature 105.5; pulse 110. Slimy, mucilaginous saliva. Urine almost suppressed. Marked headaches, sleeplessness, delirium and hallucinations, general erythema and vesicle formation. Duration of first paroxysm, two weeks. After short interval recurrence lasting two months.

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14. Watson: New York Jour. Med. and Surg., 1840, iii, 363.
15. Packard: Philadelphia Med. Times, 1872, ii, 408.
16. Earle: Chicago Med. Examiner, 1872, xiii, 3.
17. Reece: Chicago Med. Examiner, 1872, xiii, 5.

General edema and rapid emaciation. After four months lung signs appeared and death occurred. No urine examination. Death apparently due to nephritis, but whether exacerbation of an old nephritis or whether acute nephritis following the rat-bite, not determined.

CASE 30 (Banker, 1886).—Woman, aged 35, bitten on hand. After three days pain in wound; after ninth day soreness and swelling of finger; marked lymphangitis. Incision of local site; no pus obtained. Induration, swelling and lymphangitis persisted for two months. Atrophy and hemiplegia of same extremity occurred, atrophy remaining almost permanently. Persistent neuralgic pains occurred down arm indefinitely afterwards.

CASE 31 (Banker, 1886).—Woman, finger; incubation period ten days; purplish vesicle appeared locally; typical course and symptomatology. Secretions noted as being checked. Marked sleeplessness; occurrence of generalized erythema. Course four weeks; no relapses.

CASE 32 (Banker, 1886).—Woman, aged 70, bitten on hand; five days' incubation; wound did not heal for six months; constant sloughing; early dropsical symptoms; death. No necropsy.

CASE 33 (Cook,[18] 1885).—Boy, aged 11, bitten on right hand by an enraged and caged animal. Incubation two weeks. Generalized edema. Marked lymphangitis. Generalized purplish erythema. Fever and diarrhea. General enlargement of all glands of body. Result, recovery.

CASE 34 (Evans,[19] 1901).—Boy, aged 8, hand; incubation period two weeks; local and general reaction lasting one day only. After this, every week for nine weeks had recurrence of fever and constitutional symptoms lasting two to three days. Third week appearance of general erythema. Hemoglobin, 70 per cent.; red blood-cells, 4,200,000; white blood-cells, 16,200; polymorphonuclears, 87 per cent.; lymphocytes, 8.5 per cent.; eosinphils, 5 per cent.; blood-culture, *Bacillus subtilis*. Course, recovery.

CASES 35 AND 36 (Evans, 1901).—Girls, aged 12 and 9 years, bitten at same time by same rat. Three weeks later on same day both took sick, temperature 105 F.; both seats of injury swollen. Older child for four weeks had paroxysms lasting one day, with local swelling, fever and erythema; younger child had continuous fever for six weeks, then intermission first of one, then of a few days, then of a week; well in four months; marked exhaustion following.

CASE 37 (Wilcox,[20] 1839).—Man, aged 40; bitten on root of thumb; incubation twelve to thirteen days; three paroxysms, lasting four to five days each, with four days free interval; subjective symptoms very severe, with delirium. Constipation noted. Local slough of bite. Recovery.

CASES 38 AND 39 (Gilliam,[21] 1869).—Mother and son, both bitten by rat at night. Superficial abrasion; two weeks' incubation. Child showed swelling of finger and fever. Two days later similar symptoms noted in mother. Mother's finger advanced to slough, finally healing. Child showed enormous tender swelling of finger, marked constitutional symptoms, irritability of stomach and intestines, erythema, blotches on skin, malaise and finally death. Child was bitten in two places, but the bite that did not bleed was the site of the inflammation.

CASE 40 (Proescher[2]).—Boy, aged 7, superficial bite on dorsum of hand; after ten days walnut sized swelling, slight tenderness. On upper and lower arm pale, bluish-red areas of regular outline; regional glands enlarged. Liver and spleen not enlarged.

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18. Cook: Indiana Med. Jour., 1912, ii, 77.
19. Evans: Tr. Chicago Path. Soc., 1901-1903, v, 298.
20. Wilcox: Am. Jour. Med. Sc., 1839, xxvi, 245.
21. Gilliam: Cincinnati Lancet and Observer, 1869, xii, 16.

Red blood-cells, 4,700,000; white blood-cells, 8,000; polymorphonuclears, 77 per cent.; eosinophils, 1.1 per cent.; myelocytes, 0.8 per cent. Wound punctured and slight bloody fluid obtained.

On twenty-first day after bite, sudden rise of temperature to 105 F., maintained for one day. Fall of temperature by crisis, and remaining at normal [caused by puncture (?)]. During fever, white blood-cells, 21,500; polymorphonuclears, 78 per cent.

Excision of wound site. Second rise of temperature to 101 F., lasting only a few hours. Arsacetin 7½ grains given hypodermically. Second injection of 15 grains given same day.

Albumin and hyaline casts in urine.

Two months later boy well, but urine still showing albumin and hyaline casts.

Pathological Examinations.—Peculiar formations in red blood-cells, contained in hemoglobin-free zone; they consist of minute formations of deep red color, refracting light. Also larger formations, 2 to 3 microns in size. In one cell, appearance of mitosis seen. No bacteria or protozoa found. Anaerobic and aerobic cultures negative. Anaerobic and aerobic cultures of tissue negative.

Pathologic Changes in Tissues: Young connective tissue elements; proliferation; endothelial cell increase, clasmocytes. Hyaline changes in walls of small blood-vessels. Tremendous number of bacteria seen in sections.

Animal Experiments.—Excised tissue inoculated into four rats with negative results. Tissue injected into guinea-pig; developed small abscess at site of inoculation and general lymph-node enlargement. Also eruption.

FRENCH CASES

Case 41 (De Micas,[22] Toulouse, 1895).—Man, aged 50, bitten on finger; same evening chill and sweat; delirium all night. Two days later very sick, dry tongue, edema of extremity. Local swelling incised; no pus obtained. Improvement in wound; edges of incision appearing bluish black and congested as if following application of a Bier bandage. Pulse rapid and small; temperature 104 F. Generalized raised eruption over body, in places vesicular; almost complete anuria, edema, delirium, lumbar pains. Tongue very dark red. Urine shows large amount of albumin. On seventh day death from uremia. No lymphangitis noted. Toxic death.

Case 42 (Millot-Carpentier,[23] Paris, 1883).—Boy, aged 20, bitten in four places by angry rat, once in arm and three on hand; very superficial, no blood drawn. On fifth day pain in hand, fever, chilliness, sweat. Small typical phlegmon appeared, disappearing after twelve days. After free interval of a few days return of local and general symptoms. Marked dysphagia. Congestion of face, intense fever, hoarseness, almost aphonia, marked salivation, paroxysms all end by crisis, progressive paroxysms milder. Paroxysms recur every third day, lasting several hours, and leaving patient markedly prostrated. Three months after bite, patient was still having occasional crises, preceded by aura or pain in finger. Large violaceous swelling of thumb; generalized ecchymotic rash over body. Characteristic is the temporary dysphagia occurring with each paroxysm.

SCOTCH CASES

Case 43 (Carter,[24] Edinburgh, 1907).—Man, aged 40, bitten on finger; wound healed. After two days incubation, redness, lymphangitis and lymphadenitis. Course very prolonged—six months. Twenty-six attacks in all; interval two

22. De Micas: Arch. méd. de Toulouse, 1895, i, 170.
23. Millot-Carpentier: Union méd., 1883, xxxviii, 1069.
24. Carter: Edinburgh Med. Jour., 1907, new series, xxi, 443.

days; duration three days. Later duration of attacks only twenty-four hours. Paroxysms characterized by languor, weakness, nausea, thirst and dry skin, ending suddenly with profuse sweat and critical drop of temperature. Early attacks associated with stiffness of arms, neck and masseter muscles. Patchy erythematous eruption on shoulders and chest during attacks, fading with disappearance of fever; spasm in throat and difficulty in swallowing complained of during attacks. Cervical lymph-nodes enlarged. Two small subcutaneous nodules noted on forearm and calves of legs, reappearing with attacks. Spleen enlarged. White blood-cells, 16,000. Blood culture negative.

ENGLISH CASES

CASE 44 (Horder,[1] 1910).—Man, aged 62, bitten on thumb, superficially; had received ferret's bite the same day. Both wounds healing without swelling. Incubation period three weeks. Induration and lymphangitis appearing about site of the rat-bite. Temperature 101 F. Malaise; duration three days. After interval of four days recurrence of paroxysms, throat husky, hands swollen, delirium; no swelling of glands; diffuse erythema; liver and spleen not enlarged. White blood-cells, 18,000. Temperature 102 F. Pulse, 84. Course, five recurrences, two or three days apart. Three-day duration. Characterized by anorexia, torpor, sore throat, hoarseness; nodule in hamstring muscle noted. Blood culture negative. Animal inoculation with blood. Excision of nodules. Urine examination, blood smear examination, all negative.

CASE 45 (Horder, 1910).—Man, aged 52, seaman, bitten on thumb; two weeks after attack recurrent paroxysms occurring every five to six days. Chills and fever. Temperature 103 F. First paroxysm severe, later milder and occurring at longer intervals. No enlargement of glands or spleen. White blood-cells, 19,000. Blood-culture and smears negative. Duration, eight weeks ending in recovery.

CASE 46 (Horder, 1910).—Man, aged 55, farmer, bitten on elbow; after twenty-eight days, fever; duration four months, characterized by periodic recurrences of fever; no skin eruption.

CASE 47 (Middleton[9]).—Girl, aged 3; left hand bitten while asleep; incubation period of fourteen days followed by swelling of wound and a lump in axilla. Febrile paroxysms lasting forty-eight hours, with sweating, prostration; no pain. Before each paroxysm, swelling of wound and glands. Interval between attacks two or three days. Temperature 105.4 at the highest. Eight attacks in all; never less than two days in duration. Red, patchy, measly rash over cheeks, forehead and legs with the attacks. Eventually well.

Blood examinations negative, except for diplococci found on one occasion. Diplococci also found in one instance in blood culture. Organism not studied.

CASE 48 (Nicholson[25]).—Boy, aged 10, trifling bite on left hand; five weeks of careful medical attention. Then urticaria of legs, body and face. Swelling of back of arm, hand and elbow; no pus found. Antistreptococcus serum used without visible result. Course almost five months; irregular paroxysms lasting one to two days; one lasting fourteen days. Gradual diminution of strength of attacks. Well.

CASE 49 (Hewlett and Rodman[26]).—Man, aged 23, bitten on left finger; two months later development of axillary gland. Fever every five days, recurring for seventeen weeks. Duration of paroxysm from two to five days. Fall of temperature by crisis. Erythematous rash on chest and arms. Glands in axilla and groin.

Blood examination and blood-culture negative for parasites.

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25. Nicholson: Practitioner, 1913, xci, 429.
26. Hewlett and Rodman: Practitioner, 1913, xci, 86.

CASE 50 (Cruikshank[27])—Man, aged 51; bitten on finger. Sucked wound. Rat said to be "mangy" or sick. Thirteen days later bluish discoloration, then almost black. Brawny induration; tenderness, no fever; purplish rash on arm. Gangrene of entire finger; amputation required; healing took place.

Eight days after operation, or twenty-eight days after bite, headache, fever chilliness, nausea, and purplish rash again appears on arm. Temperature from 99 to 102 F. Delirium. In fifteen weeks fifteen attacks. Periods between attacks from five to eleven days. Paroxysms three days in duration. Urine negative. Convalescence very slow; after six months still unable to get about.

CASE 51 (O'Carroll[28]).—Man, aged 36; bitten on lower lip while asleep; moderate bleeding. Two days later lip swollen, edematous, purple. Seven days after this, admitted to hospital. Huge edema of lip, chin, etc. Submaxillary and sublingual glands enlarged and tender. Relapsing type of fever established; duration of fever from three to four days. Intervals from three to four days; irregular temperature; highest 103.8 F., subnormal usually after cessation of relapse. During fever, malaise for six weeks. When discharged from hospital urine negative. Developed edema of legs and face. Albumin and hyaline and granular casts with red and white blood-cells in urine. Pale, marked secondary anemia; pronounced emaciation. Parenchymatous nephritis present.

White blood-cells, 7,200; polymorphonuclears, 88 per cent.; eosinophils, 15 per cent.; myelocytes, 1 per cent.

Four months after bite, anemia and nephritis were marked; pleural cavities aspirated and clear fluid obtained. Improvement began soon after, and one year later entirely well.

Five weeks after inoculation animal killed. Necropsy showed lymph-gland enlargement, no bacteria or protozoa.

ITALIAN CASES

CASE 52 (Frugoni[2]).—Farmer, aged 54, deeply bitten on thumb; wound healed in three days. After fifteen days, sensitive red swelling of wound, breaking down to a small ulcer. Entire thumb much swollen. Chill, vomiting, fever, headache. Irregular remittent fever lasting fifteen days. Axillary and inguinal glands already swollen; large wine red spots appear on extremities. Skin infiltrated and elastic; painless.

Free interval of from twenty to thirty days.

Reappearance of fever at irregular intervals during one year. At end of year, reappearance of skin manifestations with much weakness and severe cramps in calves of legs. Same attack again in five months and again in one year. Sudden right-sided exophthalmos two and one-half years after bite. Enlargement of glands, erythematous exudation, fever; exophthalmos marked, injection of conjunctival vessels, chemosis, sight good, fundus oculi, negative. Urine negative. Red blood-cells, 3,100,000; hemoglobin, 70 per cent.; white blood-cells, 8,700; polymorphonuclears, 60 per cent.; eosinophils, 8 per cent.; mononuclears, 10 per cent.; lymphocytes, 22 per cent. No parasites. Eosinophilia later, 11 per cent. Exophthalmos disappeared slowly. Wassermann, blood and stool negative.

Patient became and remained apyrexial.

Returned later with new eruption. One erythematous spot punctured; spreads negative. Cultures negative. Cure.

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27. Cruikshank: Brit. Med. Jour., 1912, ii, 1437.
28. O'Carroll, Joseph: Dublin Jour. Med. Sc., 1912, cxxxiii, 214.

ADDENDUM

The following case[29] while appearing too late to receive mention in the text, has been added because of its unusual interest:

Hindoo woman, bitten eight years ago on right ear; ulcer of ear for three months. Fourteen days after bite, attacks began to occur, three to seven days in duration, continuing to the present time. Temperature to 105 F. Anemia and puffiness of face. Rash, glands, nephritis, and erythrocytes in urine. Wassermann negative.

Neosalvarsan 0.7 gm. given intramuscularly. After one week patient was well; no more attacks.

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29. Surveyor: Lancet, London, 1913, clxxxv, 1764.

FACTORS INVOLVED IN SOME CASES OF PLEURAL FLUID ASSOCIATED WITH NORMAL OR INCREASED VOCAL RESONANCE *

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Of the many complicated problems in the field of the mechanism of the physical signs of the respiratory system, perhaps none has been so admittedly puzzling, particularly in adults, as that of the normal or increased vocal resonance sometimes encountered in cases of pleural effusion. Skoda thought he had solved the riddle by attributing the phenomenon to what he calls consonance, but his explanation is untenable. The literature on the subject is, for the most part, rather suggestive than really helpful. Walshe's statement is: "Sometimes explicable by solid adhesions conveying the vibrations from the lung to the chest wall; in other instances the anomaly does not admit of explanation."

In trying to obtain any explanation — and only one will be offered here — for the occurrence of normal or increased vocal resonance in cases of pleural effusion, it is necessary first of all to have some knowledge of the factors operating in those cases of effusion in which there occurs a diminution or absence of vocal resonance. Assuming that in most cases of pleural effusion the compressed lung still retains more or less air in the alveoli, an occurrence which is certainly very often encountered, and which we find in experimentally produced effusions in which the conduction of sound is impeded more on the side with the effusion than on the normal side, it is not difficult in these cases, with some air still remaining in the lung, to locate a place where much of the loss of sound might occur, namely, at the junction of the lung with the fluid. Experimentally, it can be readily shown that a marked "break" does occur as sound passes from such an air-bearing lung to fluid. This "break" is apparently largely due to the change of mediums, the air-borne sounds within the lung having to pass from air, which is a very light medium, to fluid which is a very much more dense medium. The loss of sound is not nearly so great as it passes from the fluid to the chest wall. A second factor in diminshing the sounds after they leave the lung is that of diffusion. The intensity of the sounds immediately after entering the fluid as compared to the intensity after

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the sounds reach the chest walls is, in a general way, inversely proportionate to the area of visceral pleura exposed to the fluid in comparison to that of the parietal pleura bathed by the fluid. Recognizing the important part the lung plays in the interference with sound conduction in cases of effusion in which the vocal resonance is diminished or absent, the next logical step in trying to explain those cases exhibiting a normal or increased vocal resonance is to test out other conditions of the lung, to see if any of them might under the circumstances contribute more favorable factors to the conduction of sound.

The condition of the lung offering perhaps the most marked contrast to the air-bearing lung is the completely solidified lung. Having no case to report in which the patient presented before death a normal or increased vocal resonance, and at necropsy a "solid" lung surrounded by fluid, we are obliged to resort to other means for determining whether a "solid" lung would be favorable to the conduction of sound in cases of pleural effusion.

Our most illuminating experiments along this line have been with the chests of fetal calves near term. The alveoli in such animals being free from air, we are enabled to deal with one type of "solid" lung. Sounds introduced into the trachea of such an animal reach the external chest surface with great distinctness. If fluid is introduced into the pleural cavity of a fetal calf till it is completely filled, the sounds at the periphery of the chest will be found to have undergone comparatively little change, being still very distinct, while if the water in the pleural cavity is replaced by air, the sounds at the external chest surface will be found to have undergone a very marked diminution. If the fetal chest contains fluid and the lung is inflated, the sounds at the periphery of the chest will be found to be much weaker than while the lung was still air-free.

An experiment comparable to the foregoing with comparable results can be performed with the fetal lung outside the body. If the fetal lung is submerged in a vessel containing water, and sounds are introduced into the trachea and if a stethoscope is used, the mouth of the bell being tightly covered with a piece of liver to represent chest wall, and if this liver is likewise placed in contact with the water, but at no point touching the lung, the sounds will be heard with great distinctness after having passed through fetal lung, water and liver. Very much weaker sounds will be obtained if the fetal lung is replaced by an air-bearing lung.

Another experiment closely resembling the preceding ones can be made by replacing, in the last experiment, the fetal lung by a heart. Sounds after entering the aorta and passing through the cardiac walls,

the fluid and the liver covering the inferior opening of the stethoscope, still retain considerable intensity.

One can readily become convinced of the facility with which sounds pass from "solid" tissue to water by applying a suitable cylinder to the chest wall of a living human being and inserting water into this cylinder so that it is in contact with the chest wall, while the opposite end of the cylinder is tightly joined to the bell of the stethoscope. The vocal resonance and the respiratory murmur, though diminished, will be very distinctly audible.

How closely do our experiments parallel conditions that may occur in the human subject? In each experiment except the last, as contrasted with the human being, there are three things to be compared: the chest wall (or its representative, liver), the fluid and the lung. The fetal calf's chest wall corresponds sufficiently closely to the adult chest wall. Even if it is, so to spreak, made thicker by overlaying it with liver, much of the sound intensity is retained. As for the fluid, conditions are relatively much alike in both the experiments and in the supposed clinical case. The amount of diffusion by the fluid may be alike in both cases. Any striking difference, then, in the acoustic phenomena in the experiments and in human beings must relate to the lungs themselves.

The great bulk of the soft cellular tissues, whether normal, inflammatory, or malignant, apart from their fluid contents, is composed of substances known as gels. These gels, of which gelatin in a 10 or 20 per cent. strength in the firm state is an example in pure form, are closely allied in their general physical characteristics, and one would expect this similarity to extend to their acoustic properties. This has been just what has occurred in all our experimental work. We have had sufficient material for experimentation in the shape of fetal lung, liver, and muscle, and though more restricted in obtaining "solid" material from hepatized lungs, experimentation and inference show that such diseased tissue in its sound-conducting properties closely resembles the soft tissues of the body, including the fetal lung.

All our evidence indicates that these various substances, liver, muscle, fetal lung, and hepatized lung greatly resemble one another in the following particulars: They are all fairly good conductors of sound. In a general way they considerably resemble one another in their conductivity of sound. When one or more of these materials are placed in apposition the resultant effect on sound conduction is much the same as if a similar amount of any single one of these materials had been used, indicating that no serious "break" occurs as sound passes from one of these substances to another. Finally, in their relation to air and water they all resemble one another closely; that is,

there is a marked loss of sound as it passes from air to any of these substances, while there is very much less loss of sound as it passes from these various substances to air, and the passage of sound from these substances to water or in the reverse direction is attended with no serious loss of sound due to the change of mediums, because they are not of sufficiently different densities. We conclude, therefore, that these various materials, liver, muscle, fetal lung, and hepatized lung, may be considered for our purposes to be one single medium, and to act practically alike in their relation to sound conduction, whether by themselves or in association with other mediums.

While our chain of evidence is not absolutely complete as far as the lung affected with solid infiltration is concerned, all available evidence indicates that it corresponds acoustically to fetal lung and other gels.

The fluid contents of these various substances does not materially affect their conductivity.

When a pleural effusion exists there may be associated either one of two types of "solid" lung; first, that in which there is no infiltrative process, but from which the air has disappeared as the result of pressure or absorption, leaving a lung closely resembling the fetal type; and, secondly, the lung which is "solid" as the result of inflammatory or malignant change. The airless but otherwise normal lung would, on account of its smaller bulk, probably offer more favorable opportunities for sound conduction than a hepatized lung, provided that in the two cases the bronchi were equally patulous.

It is possible, according to Skoda, for only a portion of a lung to become airless as a result of an effusion, and to sink beneath the surface of the fluid.

If our conclusion is correct, that the tissue of a lung "solid" either from compression or actual pulmonary disease closely resembles fetal lung tissue acoustically, it is clear how the vocal resonance might be normal or increased in cases of pleural effusion. An increase in the vocal resonance in cases of consolidation of the lung is the usual clinical finding, and as long as the bronchi remain patulous the mere presence of fluid between the "solid" lung and the chest wall should not very materially affect the transmission of sounds, except through diffusion, though the change of medium from "solid" to fluid, and from fluid to "solid," would exert more or less of an effect. The reasons that no great change except that due to diffusion should take place are, first, that water itself is a good conductor of sound, and, secondly, that sound vibrations do not suffer greatly in intensity as they pass from "solid" tissue to water or from water to "solid" tissue. This latter fact might be expected to occur, because water and "solid" tissue do not differ greatly in density; but the same thing can be readily demon-

strated by a great variety of experiments, such as those of the fetal calf and the others presented above.

Our conception, then, of what we believe occurs in some cases of pleural effusion with a normal or increased vocal resonance may be summarized as follows: The sounds reach the surface of the "solid" lung with a certain degree of intensity, which is naturally greater than would be encountered at the external chest surface in a case of pneumonia without effusion, because the sound has not yet passed through the chest wall. The intensity of sound at the lung surface will vary to some extent with the amount of lung tissue that is traversed, so that we would expect to find louder sounds at the surface of a lung that is airless as a result of compression than in one that is "solid" from infiltration. The vibrations then enter the fluid, and do this without any serious "break" as a result of the change of medium. In their course through the fluid comparatively little sound is lost except that due to diffusion, because of the excellent conducting properties of fluid. Finally, the vibrations enter the chest wall, and again effect a transfer of medium without great loss of intensity. In other words, the interference in sound conduction is not very greatly different, as a result of the fluid in the pleural cavity, from a case presenting a "solid" lung without any effusion, provided the bronchi remain patulous, except for the loss due to diffusion. It is certainly true that the conditions for sound transmission are much better in a case with a "solid" lung surrounded by fluid than in a case of effusion in which the lung still contains air, or in a case of pneumothorax, whether the lung is either "solid" or air-bearing, provided there is no perforation from the lung into the pleural cavity.

If our explanation is correct, why does not this phenomenon occur oftener? As a matter of fact, it is impossible to state just how often a normal or increased vocal resonance does occur in cases of pleural effusion. Small basal accumulations of fluid overlying "solid" lung giving a normal or increased vocal resonance, are probably not very rare. As to the actual causes for the infrequency of the phenomenon, they may be considered to lie chiefly in the lung substance or in the bronchi. We have already spoken of the marked loss of sound that occurs when a lung, still retaining air in the parenchyma, is in contact with fluid. Interference with sound transmission from bronchial obstruction might, theoretically, be caused either by pressure from without, thus bringing the bronchial walls in apposition, or by edema or other abnormal fluid within the bronchi, which, through the action of fluid, or fluid and air, that is, froth, would occasion an intrabronchial obstruction to the passage of sounds.

Our conclusions are offered in explanation of only some of the cases of pleural effusion manifesting a normal or increased vocal resonance, for we do not believe the explanation holds good in all cases, and especially in children we believe that other causes may operate.

The loss in intensity due to diffusion in both the air-bearing and "solid" lungs will be rendered less by whatever allows the lung to approach closer to the chest wall.

The conclusions apply to various forms of fluid in the pleural cavity, whether serous, purulent or hemorrhagic (fluid blood).

The experimental evidence on which the conclusions are based has been reduced to a minimum amount of space, but we trust that it is sufficient to elucidate the subject in hand. The experiments in full will be given elsewhere.

This subject has clinical as well as theoretical interest. Thus, in any case of a doubtful nature presenting a normal or increased vocal resonance, the idea of fluid in the pleural cavity should be entertained; and, given a case with demonstrable fluid in the pleural cavity exhibiting clinically a normal or increased vocal resonance, the possibility of there being "solid" lung beyond the fluid should be borne in mind. While in some cases such a "solid" lung may be simply a compressed and airless lung, the other alternative is also to be considered, that the lung may be affected with inflammatory or malignant disease. If the condition is a recent one, recently developed consolidation of the lung in addition to the fluid is to be suspected.

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THE RELATION OF URIC ACID TO GOUTY ATTACKS*

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The work recorded in the present paper, although begun with another purpose in mind, is the result of an attempt to find *if there is any relation between attacks of gout and the amount of uric acid in the blood, or between such attacks and the amount of uric acid excreted in twenty-four hours.* By means of the new method of Folin[1] the surmises of earlier investigators that the uric acid content of the blood is increased in gout has been confirmed by Dr. Folin[2] and coworkers in a certain number of cases. These findings, taken together with observations showing a retardation of uric acid in gout, are in accord with the hypothesis of Gerrod[3] that the attacks of gout are due to increase of the uric acid content of the blood above its saturation point as a result of the inability of the kidney to excrete uric acid. Our original point, one in practical therapeutics, was to determine how we could influence the metabolic perversion, especially by dietetic measures. When our preliminary observations did not show a greater amount of uric acid in the blood of gouty patients than in normal subjects, nor any relation between uric acid excretion and the attacks of gout, and finally, showed that attacks of gout appeared even when we artificially lowered the uric acid content of the blood with atophan, we gave up our original purpose in order to reexamine carefully these points concerning the relation of uric acid excretion to gout.

The investigation was carried out on two women, Mrs. W. and Mrs. L., both of whom gave typical histories of gout — repeated sudden afebrile attacks of swelling, pain, heat and redness localized in one or more joints, which gradually subsided after several hours — and on Roentgen-ray examination showed bony changes — Bruce's nodes — characteristic of gout. It is important to emphasize that these patients were not cases of atrophic arthritis or hypertrophic arthritis, or infectious arthritis, but cases of real gout, carefully selected after consultation with our orthopedists.

Throughout the investigation the patients were kept on an approximately constant, purin-free diet — 54.8 gm. protein, 67.5 gm. fat and

* Submitted for publication Jan. 19, 1915.

1. Folin and Denis: Jour. Biol. Chem., 1913, xiii, 469.
2. Folin and Lyman: Jour. Pharm. and Exper. Therap., 1913, iv, 539.
3. Gerrod, A.: The Nature and Treatment of Gout and Rheumatic Gout, London, 1859.

167.5 gm. carbohydrate, a total of 1,496 calories — sufficient to maintain the patient's weight. The diet was made up of 150 gm. bread, 136 gm. egg, 526 gm. milk, 13 gm. butter, 120 gm. potatoes, 29 gm. rice, 20 gm. sugar, 2 slices cucumber and 2 leaves of lettuce per day. These raw materials, given in the form of a prescription to the dietetic department of the hospital, were used as the basis of menus which made a very attractive and varied diet for the patients. We would like to call especial attention to this method of prescribing a very strict, weighed diet over a long period, with entire satisfaction to the patient. By cooperation of chemist and dietitian both scientific accuracy and palatability can be obtained. One of our patients was confined to bed on account of an old ununited fracture; the other sat up part of the day.

After the preliminary work showed that the excretion of uric acid and creatinin was to be the object of our study, it was appreciated that criticism might be made of the completeness of the twenty-four-hour urinary specimens. Great care, therefore, was directed to this point. Satisfactory collections of complete twenty-four-hour quantities of urine, though seemingly a very simple matter, is in actual hospital practice exceedingly difficult. The constancy of the creatinin and uric acid determinations in twenty-four-hour quantities of urine collected from other patients as well as the constancy of the uric acid output in our patients when no drug was being given (Mrs. W., days 15 to 40) convinced us that we were surprisingly successful in our efforts. For this we have to thank the executive department of the hospital for unusually active cooperation and every facility for the strictest supervision of the patients. The patients and nurses were interested and cooperated with us completely in the work. The patients were kept in a small room by themselves and one of the nurses volunteered twenty-four-hour duty, sleeping in the same room and never leaving the patients. Even the small quantities of urine usually unavoidably lost with the feces were collected, thanks to nurse and patients. The urines were preserved with thymol and chloroform (5 c.c. chloroform and 5 c.c. of 5 per cent. thymol solution to each 1,000 c.c. of urine).

The uric acid in the blood was determined by Folin's method. A small, hollow, sterile needle about a millimeter in diameter, which had been rinsed with a solution of paraffin in ether, was inserted into the vein at the bend of the elbow and the blood allowed to flow directly into a weighed 50 c.c. Erlenmeyer flask containing 0.1 gm. potassium oxalate. This proved to be a simple method, which avoided transferring the blood from a syringe. By this means a better flow of blood was obtained with less danger of clotting than when suction of any kind was used. A tourniquet, made of a piece of rubber tubing or a

TABLE 1.—URIC ACID, CREATININ, AND CREATIN EXCRETION OF A GOUTY PATIENT

Mrs. W., weight 59.1 kilos.

Day	Urine						Blood		Attacks
	Total Quantity	Sp. Gr.	Total Nitrogen, Gm.	Uric Acid, Gm.	Creatinin, Gm.	Creatin as Creatinin, Gm.	Uric Acid Mg. Per 100 Gm.	Atophan* No. Doses Daily	
Preliminary	....	.....	.....	.....	.....	....	....	.....	Severe in finger and wrist joints.
1	968	1.016	2.36	0.186	0.374				
2	1,120	1.01	5.64	0.300	0.412	....	Taken at 12 m. 2.10	2†	
3	670	1.012	5.26	0.314	0.45	....	....	6	
4	840	1.01	6.40	0.225	0.349	....	....	6	
5	1,270	1.011	6.40	0.408	0.512	....	0.06	6	
6	900	1.008	2.58	0.132	0.187	....	....	6	
7	720	1.011	3.43	**0.196**	**0.324**	....	....	6	Attack beginning 9 a. m., lasting till p. m. Left fingers and wrist.
8, 9, and 10:	High purin diet.....							6	
11	880	1.013	4.98	0.31	0.60	....	....	6	
12	1,740	1.008	5.92	0.28	0.60	....	....	6	
13	1,060	1.013	5.04	0.36	0.72	....	....	6	
14	1,060	1.012	5.44	0.38	0.46	....	....	3	
15	1,020	1.016	6.33	**0.316**	**0.693**	....	....	0	Moderately severe attack 7 a. m. - 10 a. m. Left wrist and finger joints.
16	1,100	1.011	5.85	**0.233**	**0.33**	....	....	0	Attack 6 a. m. Left wrist and finger joints.
17	1,230	1.0115	6.06	**0.27**	**0.43**	....	2.02	0	Attack. Same joints.
18	1,420	1.011	7.47	0.25	0.51	....	....	0	
19	720	1.016	7.18	0.289	0.51	....	....	0	
20	1,060	1.013	7.00	0.30	0.51	....	....	0	
21	2,100	1.01	8.73	0.42	0.54	....	....	0	
22	900	1.017	7.44	0.182	0.52	....	....	0	
23	1,100	1.012	7.51	0.281	0.51	0	....	0	
24	1,140	1.01	7.32	0.30	0.48	....	....	0	
25	1,090	1.008	7.25	0.201	0.54	0	....	0	
26	990	1.008	6.67	0.264	0.52	0	....	0	
27	1,260	1.008	7.50	0.294	0.52	0	....	0	
28	1,230	1,008	6.90	**0.32**	**0.518**	**0.08**	....	0	Very moderate attack 6 a.m.-11 a.m.
29	1,120	1.01	6.64	**0.294**	**0.49**	**0.06**	....	0	Severe; went down in p. m.; on in evening and next morning.
30	1,440	1.01	7.20	**0.305**	**0.54**	**0.12**	....	0	Attack passed off about noon.
31	1,060	1.011	7.24	0.287	0.52	0.06	....	0	

* Each dose 0.5 gm. † Began 5 p. m.

TABLE 1.—(*Continued*)

Day	Urine						Blood	Atophan* No. Doses Daily	Attacks
	Total Quantity	Sp. Gr.	Total Nitrogen, Gm.	Uric Acid, Gm.	Creatinin, Gm.	Creatin as Creatinin, Gm.	Uric Acid Mg. Per 100 Gm.		
32	1,120	1.01	6.57	6.261	0.51	0.07	....	0	
33	1,260	1.01	6.94	0.284	0.51	0	....	0	
34	1,000	1.01	6.44	0.284	0.49	0	....	0	
35	1,040	1.011	7.40	**0.28**	**0.51**	**0.05**	....	0	Moderate attack; rubbing relieved pain.
36	1,260	1.009	6.63	**0.27**	**0.51**	**0**	....	0	Moderate attack 8 a. m.
37	1,060	1.012	6.36	0.297	0.61	0	....	0	
38	1,140	1.012	6.80	0.29	0.60	0	....	0	
39	1,290	1.012	7.94	**0.29**	**0.54**	**0**	....	0	Slight in left wrist; disappears when rubbed.
40	1,180	1.011	7.32	**0.25**	**0.53**	**0.058**	....	0	Severe pain in both wrists in p. m.; swollen and red.
41	1,610	1.01	7.27	0.28	0.52	0	....	3	
42	1,400	1.011	7.36	0.58	0.51	0.09	....	6	
43	1,220	1.008	4.50	0.23	0.38	0.02	....	6	
44	1,390	1.012	6.72	0.23	0.60	0	....	6	
45	1,700	1.01	6.59	0.24	0.69	0	....	6	
46	1,400	1.012	7.30	**0.32**	**0.71**	0	0.95	6	Severe pain in both hands and wrists. Began in night and continued next day.
47	1,300	1.011	7.80	**0.32**	**0.73**	0	....	6	Attack somewhat less severe than on previous day.
48	690	1.018	6.03	**0.30**	**0.57**	0	....	6	Attack less severe than previous day.
49	780	1.013	5.40	0.27	0.50	0	....	6	
50	900	1.012	7.30	0.25	0.57	0	....	6	

* Each dose 0.5 gm. † Began 5 p. m.

towel, was sometimes used to increase the flow of blood; gentle massage of the forearm was also helpful in increasing the blood flow. Two samples of blood, approximately 20 gm. each, were collected for analysis. The oxalate was at once dissolved by shaking, and the blood and flask weighed.

The uric acid, creatinin and creatin in the urine were determined by Folin's methods, the nitrogen in the urine by Kjeldahl's method.

The results are given in the accompanying tables.

DISCUSSION OF THE RESULTS

Uric Acid in the Blood.—The amount of uric acid in the blood of Mrs. W. on day 2 was 2.10 mg. in 100 gm. (2.11 mg. in Sample A, and

2.09 mg. in B). This blood was taken during a period free from attack and before atophan had been administered. On day 17 blood was taken during an attack. This contained 2.02 mg. in 100 gm. (Sample A, 1.99 mg.; Sample B, 2.05 mg). The uric acid in the blood of Mrs. L. was found to be 0.91 mg. per 100 gm. (Sample A, 0.87 mg.; Sample B, 0.94 mg.). From our own unpublished results and those of other investigators (Folin,[1] McLester,[4] Kocher[5]) we may assume that the normal amount of uric acid in the blood is about 2.00 mg. (0.5 to 2.9 mg.) in 100 gm. It should be observed that *in neither of our gouty patients was the uric acid content of the blood higher than that of normal individuals.* In one case it was distinctly low. Furthermore, *the amount of uric acid in the blood was the same during an acute attack as during a period free from attack.* Atophan (in 0.5 gm. doses six times a day) was administered from Day 2 to Day 14. The uric acid excretion increased, the amount of uric acid in the blood decreased to 0.66 mg. in 100 gm. (Sample A, 0.67 mg., Sample B, 0.65 mg.). These results following the use of atophan are comparable with those of other investigators. But notwithstanding the decreased content of the blood in uric acid there was a severe attack of gout on Day 7. These findings were confirmed by later findings. Atophan was given from Day 41 to Day 50. On Day 46 there was a severe attack followed by a less severe attack on two successive days. During the first day of atophan treatment the uric acid excretion was increased from 0.28 gm. to 0.58 gm. The amount in the blood fell to 0.95 mg. in 100 gm. of blood (Sample A, 0.94 mg.; Sample B, 0.95 mg.). In both of these cases it is important to emphasize that during atophan treatment we made analyses of the blood and urine; and the data show that the attacks came on *in spite of the fact that the uric acid content of the blood had been lowered* as a result of an artificial increase in the elimination.

Effect of Attack on Elimination of Uric Acid.—If the uric acid excretion (Mrs. W.) from Day 15 to Day 40, a period of twenty-five days when no atophan was being taken, is examined, it will be seen to be constant from day to day.[6] *During this period of twenty-five days with a constancy in the daily excretion of uric acid there were three attacks of gout.* In the case of Mrs. L. the uric acid likewise remained constant during the one attack (Day 21 and Day 22) which she suffered while under investigation.

4. McLester: THE ARCHIVES INT. MED., 1913, xii, 739.
5. Kocher: Deutsch. Arch. f. klin. Med., 1914, cxv, 380.
6. Except Days 21 and 22. The creatinin is so constant on these two days that one can hardly suspect any loss of specimen. The uric acid excretion for the two days taken together is 0.60, twice the usual amount for one day. A slight retention of uric acid on one day would explain the result.

It is difficult to see how the commonly accepted hypothesis of Gerrod that gout is due to the precipitation of uric acid from the blood supersaturated with this compound as a result of faulty excretion by the kidneys, or the related hypothesis that acute attacks of

TABLE 2.—Uric Acid, Creatinin, and Creatin Excretion of a Gouty Patient

Mrs. L., weight 43.2 kilos.

Day	Urine						Blood	
	Total Quantity	Sp. Gr.	Total Nitrogen, Gm.	Uric Acid, Gm.	Creatinin, Gm.	Creatin as Creatinin, Gm.	Uric Acid Mg. Per 100 Gm.	
Preliminary								
1	890	1.011	6.52	0.289	0.58			
2	710	1.016	7.57	0.268	0.63			
3	580	1.022	8.38	0.280	0.69	....	0.91	
4	800	1.018	8.48	0.32	0.67	0.38		
5	820	1.017	7.70	0.32	0.63	0.37		
6	600	1.02	7.96	0.34	0.64	0.36		
7	740	1.02	7.98	0.299	0.63	0.34		
8	660	1.023	7.92	0.446	0.98			
9	520	1.024	7.94	0.365	0.69			
10	460	1.024	7.56	0.332	0.68			
11	590	1.02	7.70	0.33	0.67			
12	900	1.016	7.94	0.328	0.69			
13	830	1.012	7.90	0.34	0.76			
14	720	1.022	8.12	0.354	0.70			
15	1,180	1.015	8.25	0.377	0.648			
16	1,290	1.02	7.86	0.35	0.61	0.14	....	Potassium citrate, 3 doses 4 gm. each.
17	840	1.02	7.52	0.33	0.66	0.31	....	Potassium citrate, 3 doses 4 gm. each.
18	1,200	1,012	7.44	0.297	0.56	0.14	....	Hydrochloric acid 0.5% solution, 3 doses 100 c.c. each.
19	1,480	1.012	8.34	0.31	0.66	0.15	....	Hydrochloric acid 0.5% solution, 3 doses 100 c.c. each.
20	1.000	1.014	7.97	0.32	0.78	0.09	....	Hydrochloric acid 0.5% solution, 3 doses 100 c.c. each.
21	900	1.016	7.89	0.24	0.78	0.18	....	Attack moderately severe.
22	....	.....	.....	.....	.....	....	....	Attack continued; much less severe in p. m.

gout are due to occasional increase of the uric acid content of the blood following intermittent impermeability of the kidney, can be harmonized with our findings.

Certain points of minor interest, which we hope to investigate further, are also to be noted:

1. Examination of the creatinin excretion of Mrs. W. from Day 18 to Day 40 shows that the creatinin excretion is not greatly affected during acute attacks of gout.

2. Atophan appears to affect the creatinin excretion. After administration (Mrs. W.) the *rise and fall* in the uric acid excretion is immediately followed by a *fall and rise* in the creatinin excretion (see Days 6 to 13 and Days 43 to 47); the creatinin excretion goes up as the uric acid goes down.

3. The creatinin excretion of one of our patients (Mrs. L.) was conspicuously irregular, varying from 0.58 gm. to 0.98 gm.

4. Creatin was occasionally present in small amounts in the urine of Mrs. W. and in large amounts in the urine of Mrs. L.

5. On Days 16 and 17, Mrs. L. was given moderately large quantities of alkali — sufficient to change the reaction of the urine from acidic to basic, and on Days 18 to 23 moderately large quantities of acid (for purposes unconnected with the present problem), with no effect in either case.

This disposes of the contention of Haig and others that alkali administration, by making the blood a better solvent for uric acid, leads to a sweeping out of increased quantities of uric acid in the blood, and that acid administration, by precipitating the uric acid from the blood into the tissues, decreases the uric acid excretion.

SUMMARY

The striking points in our data in two cases of gout are as follows:

1. There was no more uric acid in the blood than in blood of normal individuals.

2. The amount of uric acid in the blood was not altered during acute attacks of gout.

3. Uric acid excretion was not altered during acute attacks of gout.

4. Attacks of gout appeared during atophan administration, when, as shown by chemical analysis, the uric acid content of the blood had been greatly decreased.

In conclusion we wish to express our indebtedness to the members of the executive departments of the Robert B. Brigham Hospital, who have made this study possible.

168 Prospect Avenue, Madison, Wis.—Robert B. Brigham Hospital, Boston.

STUDY XXIV: THE EFFECT OF THEOBROMIN SODIUM SALICYLATE IN ACUTE CHROMATE NEPHRITIS *

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The effect of diuretics in acute nephritis has been the subject of much theorization and of some experimental work, especially during the past few years. The meager literature on the experimental work has been so recently reviewed by Fitz[1] in his article on the "Immediate Effect of Repeated Doses of Theobromin Sodium Salicylate and Theocin in Acute Experimental Nephritis" that it does not seem worth while repeating it here. In 1913 with Dr. Christian[2] I reported the results of our experiments on the effect of theobromin sodium salicylate on the duration of life of rabbits with acute uranium nephritis, and Walker and Dawson[3] reported in the same way the effects of theocin, caffein, potassium acetate, spartein sulphate and water. More recently Dr. Christian[4] has reported the effect of theobromin sodium salicylate on renal function as measured by the excretion of phenolsulphonephthalein in acute uranium nephritis. It seemed, therefore, desirable to supplement this work of a year ago by making a study of the effect of this same diuretic in other types of acute experimental nephritis. Following the theories of Schlayer and his coworkers in the attempt to produce a vascular nephritis, arsenic acid was selected. After

* Submitted for publication Jan. 9, 1915.

* From the Laboratory of the Theory and Practice of Physic, Harvard Medical School.

* This is one of a series of studies on experimental cardio-renal disease. Study I, Smith: Boston Med. and Surg. Jour., 1908, clviii, 696; Study II, Christian: Boston Med. and Surg. Jour., 1908, clix, 8; Study III, Christian: Jour. Am. Med. Assn., 1909, liii, 1792; Studies IV-XV, Christian, Smith and Walker: THE ARCHIVES INT. MED., 1911, viii, 468-551; Study XVI, Christian and O'Hare: THE ARCHIVES INT. MED., 1913, XI, 517; Studies XVII and XVIII, O'Hare; THE ARCHIVES INT. MED., 1913, xii, 49, 61; Study XIX, Christian and O'Hare: Jour. Med. Research, 1913, xxviii, 227; Study XX, Walker and Dawson, THE ARCHIVES INT. MED., 1913, xii, 171; Study XXI, Fitz: THE ARCHIVES INT. MED., 1914, xiii, 945; Study XXII, Christian: THE ARCHIVES INT. MED., 1914, xiv, 827; Study XXIII, Fitz: THE ARCHIVES INT. MED., 1915, xv, 524.

* This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

* The theobromin sodium salicylate used was purchased under the trade name of Diuretin.

1. Fitz: THE ARCHIVES INT. MED., 1914, xiii, 945.
2. Christian and O'Hare: THE ARCHIVES INT. MED., 1913, xi, 517.
3. Walker and Dawson: THE ARCHIVES INT. MED., 1913, xii, 171.
4. Christian: THE ARCHIVES INT. MED., 1914, xiv, 827.

TABLE SHOWING EFFECT OF THEOBROMIN SODIUM SALICYLATE ON LIFE OF RABBITS WITH POTASSIUM BICHROMATE NEPHRITIS

	Rabbit No.	Weight gm.	Duration of Life After First Bichromate Injection (Days)	Average Life of Those that Died (Days)	Number Dead
Series 1—					
Potassium bichromate, 2 doses; 0.015 gm. per kg.	846	2,100	6		
	862	2,060	4	5	2
	864	2,260	17 *		
Potassium bichromate, 2 doses; 0.015 gm. per kg. Theobromin sodium salicylate, daily; 0.014 gm. per kg.	866	2,250	3		
	865	2,100	6	5⅓	3
	877	2,060	7		
Series 2—					
Potassium bichromate, 2 doses; 0.015 gm. per kg.	881	2,070	3		
	882	2,360	39 *	3	2
	885	1,780	3		
Potassium bichromate, 2 doses; 0.015 gm. per kg. Theobromin sodium salicylate, daily; 0.028 gm. per kg.	878	2,100	39 *		
	879	2,030	6	4½	2
	884	1,840	3		
Series 3—					
Potassium bichromate, 2 doses; 0.015 gm. per kg.	883	1,900	7		
	886	2,230	25 *	7	1
	889	2,060	25 *		
Potassium bichromate, 2 doses; 0.015 gm. per kg. Theobromin sodium salicylate, daily; 0.056 gm. per kg.	888	2,050	3		
	890	2,230	5	4	2
	891	2,080	25 *		
Series 4—					
Potassium bichromate, 2 doses; 0.015 gm. per kg.	893	1,790	21		
	894	2,020	27 *	21	1
	895	2,730	26 *		
Potassium bichromate, 2 doses; 0.015 gm. per kg. Theobromin sodium salicylate, daily; 0.56 gm. per kg.	896	2,350	19		
	901	2,040	18	18½	2
	902	1,880	27 *		

* Experiment discontinued.

TABLE SHOWING EFFECT OF THEOBROMIN SODIUM SALICYLATE ON LIFE OF RABBITS WITH POTASSIUM BICHROMATE NEPHRITIS—(*Continued*)

	Rabbit No.	Weight gm.	Duration of Life After First Bichromate Injection (Days)	Average Life of Those that Died (Days)	Number Dead
Series 5—					
Potassium bichromate, 2 doses; 0.0175 gm. per kg.	899	2,500	5		
	909	2,200	15 *	5	1
	915	1,750	15 *		
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Theobromin sodium salicylate, daily; 0.056 gm. per kg.	911	1,900	4		
	913	2,270	6	4⅓	3
	914	2,450	4		
Series 6					
Potassium bichromate, 2 doses; 0.0175 gm. per kg.	910	1,800	18 *		
	917	2,000	18 *	6	1
	923	2,100	6		
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Theobromin sodium salicylate, daily; 0.014 gm. per kg.	916	1,850	18 *		
	921	1,950	7	5½	2
	920	2,050	4		
Series 7—					
Potassium bichromate, 2 doses; 0.0175 gm. per kg.	925	1,920	18 *		
	930	2,820	18 *	6	1
	924	1,800	6		
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Theobromin sodium salicylate, daily; 0.028 gm. per kg.	926	2,450	2		
	927	1,980	18 *	3	2
	929	1,550	4		
Series 8—					
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Urea and salt daily	934	2,210	4		
	949	2,000	10 *	4	1
	952	1,940	10 *		
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Theobromin sodium salicylate, daily; 0.028 gm. per kg. Urea and salt daily.	944	2,070	10 *		
	947	2,240	2	3	2
	951	2,110	4		

* Experiment discontinued.

Average duration of life after first bichromate injection:
Bichromate only .....7 1/8 days
Bichromate and theobromin sodium salicylate.....6 1/16 days
Number dead:
Bichromate only 10
Bichromate and theobromin sodium salicylate.....18

much work with this drug, however, I came to the same conclusion arrived at by Fitz and others working with it, that it was not possible to control the action of arsenic so as to produce regularly a uniform, workable nephritis, and so the plan of studying the effect of diuretics on a vascular type of nephritis was given up. For the study of a tubular type of nephritis potassium bichromate, which produces lesions confined almost exclusively to the tubules, was selected as the kidney irritant.

Forty-eight normal adult rabbits, on a known diet of carrot, oats and water, were divided into eight groups of six each. These, in turn, were subdivided into "controls," which received potassium bichromate only, and so-called "diuretic" rabbits which were given, in addition, theobromin sodium salicylate. The controls and diuretic animals were paired off in each group so as to be of approximately parallel weights.

The potassium bichromate was given subcutaneously on two successive days in body weight doses. The diuretic was given in a similar manner except that it was begun on the day of the second bichromate injection and was repeated daily until the animal died or until the experiment was discontinued. The dose of the two drugs was varied in each group so as to get the effect of different dosage of the diuretic in nephritides of varying degrees of severity. (For doses used, see table.)

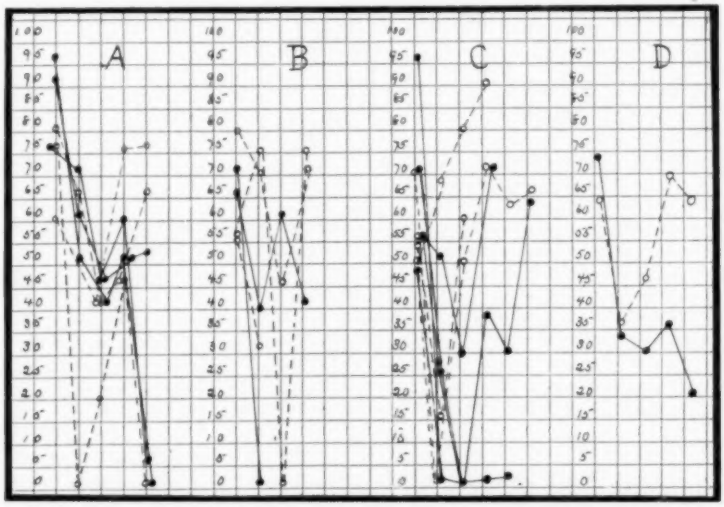
In these eight groups observations were made on the comparative length of life of control and diuretic rabbits; their comparative pathology and their comparative water excretion. In a smaller number of these rabbits a comparative study was made on the output of phenolsulphonephthalein, nitrogen and sodium chloral.

The primary object of the work was to determine whether or not theobromin sodium salicylate affected in any way the length of life of rabbits with acute chromate nephritis. Not all of the forty-eight rabbits died, but, as the table shows, of the twenty-eight that died only ten were controls, whereas eighteen, almost twice as many, had been treated with theobromin sodium salicylate. This is, I think, a rather striking result, more striking even than our results in uranium nephritis.

The average duration of life after the first dose of potassium bichromate was $6\frac{11}{16}$ days for the diuretic rabbits, and $7\frac{1}{8}$ for the controls. This too, though not so striking, is in favor of those not treated with the diuretic. These two results show rather conclusively that in this type of nephritis, as has already been shown for uranium nephritis, theobromin sodium salicylate is usually distinctly harmful. It must be said, however, that in Series 1 and 2, where small doses of bichromate and a small and medium dose, respectively, of theobromin sodium

salicylate were used, those diuretic animals that died lasted somewhat longer than the corresponding controls. This is in keeping with the results obtained previously in uranium nephritis, namely, that in mild types of nephritis small doses of theobromin sodium salicylate occasionally seem to prolong life.

No attempt was made to study the question of comparative pathology very accurately. Careful studies were made, however, of the kidneys of those rabbits that died, and the pathological picture of the controls was set off against that of the diuretic animals in the same



Dotted lines show excretion of phenolsulphonephthalein in rabbits which received potassium bichromate. Solid lines show phenolsulphonephthalein excretion in rabbits which received both potassium bichromate and theobromin sodium salicylate. *A* gives the results for rabbits 893, 894, 895, 896, 901 and 902; *B*, rabbits 924, 925, 930, 927 and 929; *C*, rabbits 931, 938, 933, 944, 939, 934, 949 and 952. (In the accompanying table is shown the dosage of drugs used and other details in regard to these rabbits.) In *D* is shown by the dotted line the average phenolsulphonephthalein excretion for all rabbits that received potassium bichromate but no diuretic, while by the solid line is shown the average excretion of those rabbits that received potassium bichromate followed by theobromin sodium salicylate.

group. This is scarcely a fair comparison. It was found, however, that the rabbits treated with the diuretic did seem to show slightly more pronounced tubular lesions.

The majority of the rabbits showed edema when examined post mortem; but, of those that did not, six were rabbits which had received the diuretic while three had not. As to the rest the amount of fluid was about the same in both divisions.

The question of change in the outflow of urine following the production of the nephritis was studied in carefully prepared intake and output charts. These showed on the whole that theobromin sodium salicylate not only did not produce any increase of water excretion, but seemed often to have caused an inhibition.

The phenolsulphonephthalein function test was performed in twenty-one animals. The results (see Chart A, B and C), though not at all uniform, show that the control rabbits (those that received the chromate but no diuretic) were less severely affected in the majority of cases, and that when they did get back to a normal output of phenolsulphonethalein they did so more quickly than the diuretic rabbits. This agrees with the results obtained by Dr. Christian. The harmful action of the diuretic drug is shown more clearly by charting the averages of the phenolsulphonephthalein output in the two groups of rabbits (see chart, D).

The nitrogen and sodium chlorid metabolism was studied in eight cases. No definite conclusions, of course, can be drawn from such a small number of cases, especially in view of the fact that the results are far from uniform. This last is true even when a fairly large amount of urea and salt was added to the daily diet to render the output more stable. Making three day averages of the output of the nitrogen and salt helps somewhat, but not greatly. The nitrogen output was measured by the Kjeldahl method, the sodium chlorid by Goodall's modification of the Volhard method. Charts of these eight cases show that in the diuretic rabbits there is usually a falling off rather than an increase in the nitrogen elimination immediately following the treatment with theobromin sodium salicylate. In the controls, on the other hand, there is, in some cases, an increase. As to the salt excretion the results are so variable that they indicate nothing.

CONCLUSIONS

In conclusion we may say that in an experimental tubular nephritis caused by potassium bichromate of a severe or moderately severe type theobromin sodium salicylate usually shortens the life of the animals; in mild cases it sometimes seems to prolong it.

On the whole, it seems to increase the lesion in the kidney and to hinder the excretion of water, phenolsulphonephthalein and possibly nitrogen.

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CERTAIN ASPECTS OF BIOLOGICAL OXIDATION*

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The subject of oxidation presents one of the most fascinating themes in the entire domain of chemistry. The various views which have been held regarding the nature of combustion and oxidation have always exercised a profound influence on chemical thought and on biological science and medicine. Modern views regarding the nature of oxidation date from the work of Lavoisier, who observed that, in the process of oxidation, oxygen adds itself to the substance oxidized, and that the resulting one or more products weigh more than the original material by exactly the weight of oxygen required to effect the oxidation.

It is not within the scope of this lecture to recount the views which have been held regarding the mechanism of oxidation in general. It would also be quite futile to review the whole subject of vital oxidation in the time at our disposal. I shall therefore confine my remarks to a small part of the field in which I have been particularly interested for several years.

The subject of vital oxidation may be divided into the following phases:

1. The mechanism by which oxidative processes are brought about in living material.
2. The nature of the substances oxidized by living organisms.
3. The relation between oxidation within the body and the energy requirements of the organism.
4. The relation of oxidative processes to other chemical processes in the body.
5. The effect of various substances and of various conditions on vital oxidation.
6. The relation of vital oxidation to functional activity.

Notwithstanding the great interest connected with the first four phases of oxidation here enumerated, I shall have very little to say regarding them except as they bear directly on the last two phases.

It was recognized by Lavoisier that oxidation is constantly occurring in the body, and it was surmised that the body derives its heat from oxidation. Ever since the establishment of the principle of

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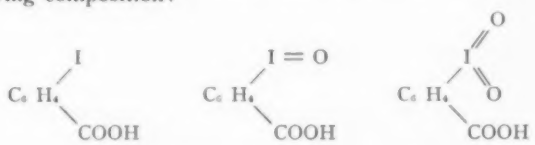
* Lecture read before the Harvey Society, New York, Nov. 8, 1914.

the conservation of energy, the body has been regarded as an engine which converts the latent chemical energy of foodstuffs by oxidation into heat, mechanical work and all the manifestations of life. Oxidation within the body was looked on for many years as quite similar to combustion outside the body. It is perfectly evident, however, that great differences exist between oxidation within and without the organism. Thus proteins, carbohydrates and fats are oxidized within the body at a temperature of 37° C., whereas it requires a far higher temperature to oxidize these substances in the air. In the attempts to explain this fact, the group of oxidizing enzymes, or oxidases, was discovered. Much work has been done to indicate the great differences between oxidation within and without the body. It has been shown that many substances which are readily oxidized outside the body are either very incompletely oxidized or not oxidized at all within the organism. Under this list may be classed carbon monoxid, oxalic acid, and many others. The selective oxidation of many organic substances in the body is another very remarkable characteristic of vital oxidation. Thus very slight changes in the structure of a substance may completely prevent its oxidation in the body. A great deal of work has been done on the relation of chemical constitution to the property of undergoing oxidation in the organism. I shall take occasion later to refer to another remarkable difference between oxidation within and without the body.

In 1901 Kastle and I[1] showed that certain of the organic peroxids give practically all of the reactions of certain oxidases widely distributed in living matter. We found, for instance, that benzoyl peroxid gives the well-known guaiacum reaction, and that the bluing of guaiacum by benzoyl peroxid can be inhibited by hydrocyanic acid in the same manner that this substance inhibits the bluing of guaiacum by the oxidases. On the basis of this work and on the presumption that the oxidases play a rôle in pathological as well as physiological processes, I was led to study the pharmacological action of benzoyl peroxid and also any therapeutic uses to which it might be put.[2] The substance proved to be markedly antiseptic and extremely useful in the treatment of local infection; in fact, its effect in local infection was so remarkable as to suggest that its beneficial effect could not be attributed entirely to its antiseptic action. This naturally suggested that the active oxygen contained in benzoyl peroxid had some peculiar effect on the tissues, increasing their resistance to infection. The nature of this increased resistance was not determined at that time. I shall refer to this again later. Benzoyl peroxid is but slightly soluble in water, so that its effect

1. Kastle and Loevenhart: Am. Chem. Jour., 1901, xxvi, 539.
2. Loevenhart: Therap. Monatsch., 1905, p. 426.

on general infections could not be studied. In casting about for a substance soluble in water which might contain oxygen in a physiologically available form, and which could be injected intravenously, it was decided to make a careful pharmacological study of the sodium salts of iodbenzoic, iodosobenzoic and iodoxybenzoic acids. These acids, which were first prepared by Victor Meyer and his co-workers,[3] have the following composition:



Iodbenzoic acid contains no active oxygen. Iodosobenzoic acid contains 6.06 per cent. of active oxygen. Iodoxybenzoic acid contains 11.43 per cent. of active oxygen. By active oxygen I mean oxygen which in the chemical sense is very active outside the body and which in the compounds under consideration is the oxygen bound to the iodin.

Grove and I[4] sought to determine whether the oxygen contained in these substances is physiologically available, that is to say, whether the oxygen bound to iodin in these substances can be utilized by the organism for purposes of physiological oxidation. We found that the sodium salts of iodosobenzoic and iodoxybenzoic acids instantly oxidize hemoglobin to oxyhemoglobin. We found that sodium iodosobenzoate can furnish the oxygen for at least one peroxidase reaction. It was found that while neither blood nor sodium iodosobenzoate is capable of oxidizing phenolphthalin to phenolphthalein, together they are capable of effecting this oxidation. Dilute solutions of sodium iodosobenzoate and sodium iodoxybenzoate taste very much like solutions of hydrogen peroxid. All of these facts indicate that the oxygen which they contain is physiologically available.

Arkin showed that sodium iodosobenzoate and sodium iodoxybenzoate are from one hundred to two hundred times as highly bactericidal as sodium iodbenzoate on *Bacillus typhosus*.[5] This difference can be attributed only to the oxidizing action of the former substances. On intravenous injection it was found that sodium iodosobenzoate and iodoxybenzoate markedly depress the respiratory and vasomotor centers, whereas the iodbenzoate has no such effect. Therefore, the effects of the two former substances on these centers must be attributed to the physiologically active oxygen which they contain. It would thus appear

3. Meyer, Victor: Ber. d. deutsch. chem. Gesellsch., 1892, xxv, 2632; 1893, xxvi, 1354, 1727; 1894, xxvii, 1600.
4. Grove and Loevenhart: Jour. Pharmacol. and exper. Therap., 1911, iii, 101.
5. Arkin: Jour. Pharmacol. and exper. Therap., 1911, iii, 145.

that a substance which apparently increases oxidation within the respiratory and vasomotor centers, depresses them. It has been known for a long time that hydrocyanic acid is one of the most powerful stimulants of the respiratory center. It is also well known that hydrocyanic acid depresses vital oxidation. Therefore it seemed interesting to determine whether an antagonism existed between the action of hydrocyanic acid and iodosobenzoate. In order to determine this, cannulas were placed in both femoral veins of a cat. In the left femoral vein a solution of sodium iodosobenzoate was injected and its effect determined. After a short time sodium cyanid was injected into the right femoral vein, in order determine the effect of a given dose in the animal under experimentation. Then both substances were injected simultaneously into the opposite veins. The complete antagonism of the two substances in their action on the respiratory center was readily seen.[6] This further indicated that iodosobenzoate increased oxidation in the center, since it was capable of antagonizing a substance known to inhibit vital oxidation.

Eyster and I[7] showed that sodium iodosobenzoate, when perfused through the isolated mammalian heart, has a marked effect on the size of the beat even in very dilute solutions, whereas iodbenzoate has very much less action. We found that most of the active oxygen of the iodosobenzoate is removed from the solution on perfusing through the heart, and that the more vigorously the heart is beating the greater is the amount of oxygen taken up by the heart from this compound. Although iodoxybenzoate is apparently as active on the respiratory center as iodosobenzoate, it is much less active in alterating the activity of the isolated heart. The heart also takes up far less oxygen from a solution of iodoxybenzoate than from iodosobenzoate, which again clearly indicates that it is the active oxygen in these compounds which accounts for their pharmacological action. It is also very interesting as showing how futile it is to predict, from knowledge previously gained with one tissue, what effect a given oxidizing substance will have on another tissue. In fact, the longer one works at the problems of vital oxidation, the less willing he becomes to make predictions. The effect of any new factor or condition cannot be foretold. It must be ascertained by experiment.

The action of iodoso- and iodoxybenzoate on the circulation and respiration seemed so interesting that we determined to step aside from the original object of the investigation, namely, the quest of a substance for the treatment of general infection, long enough to determine the relation between physiological activity and changes in the rate of

6. Grove and Loevenhart: Jour. Pharmacol. and exper. Therap., 1911, iii, 131.
7. Eyster and Loevenhart: Jour. Pharmacol. and exper. Therap., 1913, v, 21.

oxidative processes. Strange to say, this question had never been carefully attacked as such, and the knowledge on the subject, which was more or less desultory, did not elucidate the problem satisfactorily. The reaction of the animal to asphyxia has been investigated for the last sixty years. Asphyxia is, however, a complicated condition. There exists both a lack of oxygen and an excess of carbon dioxid, and the relative parts played by these two factors in producing the symptoms of asphyxia have been the source of endless controversy. Furthermore, products of incomplete oxidation having an acid character arise during asphyxia, and to these the symptoms of asphyxia have also been ascribed in part. The striking symptoms of asphyxia, however produced, are the following: increase in the rate and depth of the respiration, rise of blood pressure, slowing of the pulse, cessation of respiration, general convulsions followed by paralysis, marked and progressive fall of blood pressure, death.

I cannot review the previous work on the subject of asphyxia, and must confine myself to recounting certain experiments which seem to us to demonstrate conclusively that the symptoms of asphyxia can be brought about by decreased oxidation. Gasser and I[8] produced decreased oxidation by methods which did not permit of any accumulation of carbon dioxid or of acid products in two ways:

1. By injecting sodium cyanid intravenously.

2. By injecting pure carbon monoxid into the trachea without interfering with the respiration in any way.

Artificial respiration was given when the natural respiration was depressed, thus preventing the accumulation of carbon dioxid. In the rabbit the injection of sodium cyanid into the jugular vein stimulates the respiratory center, on the average, within three to four seconds. Stewart[9] found that it requires 2.8 seconds for the blood to pass from the left jugular vein to the right carotid in the rabbit. Thus the latent period of stimulation of the respiratory center by sodium cyanid is practically the time required for the substance to reach the center. This extremely rapid action precludes all possibility of explaining the stimulation as due to excess of carbon dioxid or the accumulation of acid products. It proves beyond peradventure that the cells respond with stimulation to a decrease in their own oxidative processes directly. Similarly, the vasomotor and cardio-inhibitory centers are stimulated, but the latent period is longer than in the case of the respiratory center. The order of stimulation is, first, respiratory center, second, the vasomotor center and last, the cardio-inhibitory center. With carbon monoxid quite similar results were obtained, but a little longer time was

8. Gasser and Loevenhart: Jour. Pharmacol. and exper. Therap., 1914, v, 239.
9. Stewart: Jour. of Physiol., 1894, xv, 4.

required. Here the stimulation of the respiratory center occurs within six and one-half seconds. The extra time required to produce stimulation by carbon monoxid can readily be accounted for by the time required for the gas to be drawn into the lungs and pass through the endothelium into the blood. The difference between the action of carbon monoxid and hydrocyanic acid in these reactions is this: The carbon monoxid by combining with hemoglobin and forming carbon monoxid hemoglobin reduces the amount of oxygen which the cells receive, whereas hydrocyanic acid does not interfere with the supply of oxygen, but interferes with the consumption of oxygen by the tissues through its inhibiting action on the oxidases. This fact illustrates that *decreased oxidation may occur when the supply of oxygen is not diminished and that the term decreased oxidation is not synonymous with oxygen want. Oxygen want is but one means of producing decreased oxidation.* Every phase of the pharmacologic action of hydrocyanic acid and carbon monoxid can be explained on this basis. These results clearly prove that decreased oxidation leads first to increased functional activity or stimulation and later to depression.

The effect of reducing oxidation in these centers depends on three factors: first, on the extent to which the oxidative processes are reduced; second, the suddenness with which they are reduced; third, the condition of the centers.[10] If oxidation is reduced below a certain level, stimulation will not be observed. The more suddenly the rate of oxidation is reduced, the greater will be the stimulation. If the reduction of the rate of oxidation is very slow no stage of stimulation will be noted, as the irritability of the cells will then decrease faster than the stimulus increases. Finally, the better the condition of the center the more readily is the stage of stimulation demonstrable and conversely, the poorer the condition of the center the more difficult it is to elicit a stage of stimulation. To summarize, then, we have found that a depression in the rate of oxidative processes in the medullary centers leads primarily to stimulation, whereas our work on iodosobenzoate and iodoxybenzoate showed that an increase in the rate of oxidative processes causes decreased activity or depression. In other words, the functional activity varies inversely with changes in the rate of oxidative processes. We[11] have attempted to form some conception which would account for this inverse relationship between functional activity and changes in the rate of oxygen utilization by the cell. Verzár,[12] working on the gaseous metabolism of muscle, and Barcroft and Piper[13] on the

10. Loevenhart: Arch. f. d. ges. Physiol. (Pflüger's), 1913, cl, 379.
11. Gasser and Loevenhart: Jour. of Pharmacol. and exper. Therap., 1914, v, 239.
12. Verzár: Jour. Physiol., 1912, xliv, 243.
13. Barcroft and Piper: Jour. of Physiol., 1912, xliv, 359.

gaseous metabolism of the submaxillary gland, have shown that the period of increased utilization of oxygen outlasts by several minutes the period of increased functional activity following stimulation. Barcroft and Piper found that following certain forms of stimulation, maximum utilization of oxygen occurs when the saliva almost ceased to flow. They say: "Probably therefore gland, like muscle, is a mechanism in which oxidation serves to replenish a store of potential energy which is liberated in the act of secretion." It would seem that we have two sets of processes going on within cells, one of which requires the acquisition of oxygen from without the cell. Since the cell continues to fix oxygen at a greatly increased rate for a time after functional activity has ceased and since heat continues to be liberated after the contraction of a muscle as shown by A. V. Hill[14] it would seem that the fixation of oxygen by the cell must be the beginning of a series of oxidations. Let us designate this phase of oxidation within the cell as the R processes, since R will suggest rest and recovery. The essential feature of the R processes is that they require oxygen from without the cell. From our point of view functional activity is the external manifestation of a set of chemical reactions occurring within the cell. Since energy is liberated during functional activity we must assume that these processes are also oxidative at least in part. Let us designate the processes of which function is the external expression as A processes, since A will suggest activity. We conceive that neither the A nor the R processes are ever in complete abeyance during life but that their relative intensity determines the relative state of activity of the cell.

The work with iodosobenzoate and iodoxybenzoate indicates that a stimulation of the R processes (oxygen fixation) retards the A processes and depression results. On the other hand, if the R processes are depressed, as by the use of carbon monoxid or sodium cyanid, it would seem that the cell must derive its energy from the A processes and increased functional activity must result. This is the only conception we have been able to form to account for the reciprocal relationship of oxygen fixation and functional activity. We know that an increase in the A processes entails an increase in the R processes, but since the latter outlast the former it would appear that the R processes lag behind. Since recuperation apparently does not occur under anesthesia, it would follow that both the A and the R processes are depressed in this state. Our work indicates also that when the R processes fall below a certain level, all functional activity ceases, or, in other words, the A processes cease. According to our point of view, the stimulating action of carbon dioxid is due to its power to depress the R processes

14. Hill, A. V.: Jour. Physiol., 1913, xlvi, 28.

just as hydrocyanic acid does. We believe that under physiological conditions the oxidative processes and therefore the functional activity of the respiratory center are conditioned by the carbon dioxid tension and not by the oxygen tension. This follows from the work of Haldane and his co-workers.

We have recently turned our attention to another phase of the proposition that decreased oxidation primarily stimulates cells. The previous work showed that the cells of the respiratory center are apparently more sensitive to alteration in the rate of their oxidative processes than any cells in the body, and respond most readily with stimulation to a decrease in their oxidative processes. This is what we should expect, since the respiratory center, by controlling the entrance of oxygen into the body and the exit of carbon dioxid, really controls one of the fundamental conditions for tissue oxidation. From the lungs to the tissues the oxygen must be carried by the hemoglobin. Since the red blood corpuscles and hemoglobin are produced by the red bone-marrow, it is obvious that the red bone-marrow supplements the action of the respiratory center in supplying the tissues with oxygen.

Paul Bert[15] thirty-six years ago showed that the oxygen carrying power of the blood increases at high altitudes. He explained this as due to a reaction of the organism to accommodate itself to the decreased pressure of oxygen in the atmosphere. The facts brought out by Bert as well as his explanation of the blood changes have been the subject of much controversy. The majority of investigators, however, have agreed with Bert that there is an increase in erythrocytes and hemoglobin at high altitude. I cannot review the views which have been held regarding these phenomena, but will merely enumerate some of them. 1. The increase is insignificant. 2. The erythrocytes and hemoglobin always increase proportionately and the increase is due to concentration of the blood either by loss of water from the body through evaporation or by the passage of plasma from the blood to the tissues. Again, the blood changes have been attributed to various physical factors such as (1) a displacement of the diaphragm upward and an alteration in the pulmonary circulation, (2) lessened vital capacity of the lungs at reduced pressure, etc. There are obviously many factors which may play a rôle in the effect of reduced atmospheric pressure on the blood. From our point of view, the increase in the hemoglobin and red blood corpuscles is probably due to a stimulation of the bone-marrow by decreased oxidation within the bone-marrow itself.

I should like to describe briefly the apparatus which Mr. A. C. Kolls and I have devised in order to attack this problem.[16] This apparatus

15. Bert, Paul: La pression barométrique, 1878, p. 1108; Compt. rend. Acad., 1882, xciv, 805.

16. A description of this apparatus will soon be published.

was devised for the purpose of keeping animals in an atmosphere of reduced oxygen tension and at the same time to maintain them at the normal atmospheric pressure and thereby exclude all of the physical factors of high altitude. It consists of a respiratory chamber, the air of which is kept at a constant composition. The arrangement for absorbing carbon dioxid and water which the animal produces is that devised by Professor Benedict,[17] and the oxygen supply is automatically controlled by a mechanism quite similar to that used in Professor Lusk's laboratory and described by Williams.[18] We have introduced certain modifications which greatly facilitate the work that we have in hand. The results which Mr. H. C. Dallwig, Mr. A. C. Kolls and I have obtained with this apparatus may be indicated by citing two or three experiments out of a large number.[19]

I. REDUCED OXYGEN EXPERIMENT

Rabbits 4 and 5

Length of experiment.....132 hours
Average oxygen tension.....11.98 per cent.
Average carbon dioxid..... 0.08 per cent.
Average per cent. humidity.... { Inside 33 per cent. / Outside 33 per cent.

	Hemoglobin G. per 100 c.c.	Erythrocytes
No. 4—Before experiment.....	13.98	6,678,000
After 132 hours.....	16.97 (+ 21.4)	8,417,000 (+ 26)
No. 5—Before experiment	14.39	8,384,000
After 132 hours.....	17.43 (+ 21)	8,490,000 (+ 1.3)

II. CONTROL EXPERIMENT

Rabbits 9, 10 and 11

Length of experiment.....167.5 hours
Average oxygen tension .....20.9 per cent.
Average carbon dioxid tension....., 0.21 per cent.

Weight
No. 9 (albino) Before control 852 gm. After 970 gm. (+ 118 gm.)
No. 10 (albino) Before control 861 gm. After 935 gm. (+ 74 gm.)
No. 11 (albino) Before control 790 gm. After 898 gm. (+108 gm.)

	Hemoglobin G. per 100 c.c.	Erythrocytes
No. 9—Before control	10.9	5,293,000
After control	11.58 (+ 6.2)	5,772,000 (+ 9)
No. 10—Before control	13.1	6,389,000
After control	13.74 (+ 4.9)	6,512,000 (+ 1.9)
No. 11—Before control	12.66	6,152,000
After control	11.54 (— 8.8)	5,827,000 (— 5.3)

17. Benedict: Deutsch. Arch. f. klin. Med., 1912, cvii, 156.
18. Williams: Jour. Biol. Chem., 1912, xii, 317.
19. A complete account of these experiments will soon be published.

III. REDUCED OXYGEN EXPERIMENT

Rabbits 9, 10 and 11

Length of experiment.....147 hours
Average oxygen tension .....10.98 per cent.
Average carbon dioxid tension..... 0.19 per cent.

Weight
No. 9—Before experiment 970 gm. After 1,060 gm. (+ 90 gm.)
No. 10—Before experiment 935 gm. After 1,070 gm. (+ 135 gm.)
No. 11—Before experiment 898 gm. After 973 gm. (+ 75 gm.)

	Hemoglobin G. per 100 c.c.	Erythrocytes
No. 9—Before experiment	11.58	5,772,000
After experiment	15.68 (+ 35.4)	7,544,000 (+ 30.7)
2 days after	16.70 (+ 44.2)	7,707,000 (+ 33.5)
10 days after	15.26 (+ 31.8)	7,442,000 (+ 28.9)
23 days after	11.8 (+ 1.9)	6,000,000 (+ 3.9)
No. 10—Before experiment	13.74	6,512,000
After experiment	16.38 (+ 19.2)	7,301,000 (+ 12.1)
2 days after	15.82 (+ 15.1)	7,186,000 (+ 10.3)
10 days after	16.76 (+ 22)	7,635,000 (+ 17.2)
23 days after	15.77 (+ 14.8)	7,533,000 (+ 15.7)
No. 11—Before experiment	11.54	5,827,000
After experiment	17.02 (+ 47.5)	7,266,000 (+ 24.7)
2 days after	14.70 (+ 27.4)	7,200,000 (+ 23.6)
10 days after	14.83 (+ 28.5)	6,918,000 (+ 18.7)
23 days after	14.47 (+ 25.4)	6,872,000 (+ 17.9)

IV. REDUCED OXYGEN EXPERIMENT

Rabbits 15 and 16

Length of experiment.....260.5 hours
Average oxygen tension .....10.6 per cent.
Average carbon dioxid tension..... 0.2 per cent.

Weight
No. 15—(Gray and white)—
Before experiment, 1,050 gm. After 1,130 gm. (+ 80 gm.)
No. 16—(Albino)—
Before experiment, 1,010 gm. After 1,150 gm. (+ 140 gm.)

	Hemoglobin G. per 100 c.c.	Erythrocytes
No. 15—Before experiment	10.6	5,376,000
3 days' run	13.32 (+ 25.7)	5,920,000 (+ 10.10)
6 days' run	16.76 (+ 58.1)	6,620,000 (+ 23.1)
11 days' run	15.92 (+ 50.2)	5,715,000 (+ 6.3)
No. 16—Before experiment	11.16	5,952,000
3 days' run	12.28 (+ 10)	6,075,000 (+ 2.1)
6 days' run	14.96 (+ 34)	7,018,000 (+ 17.9)
11 days' run	15.26 (+ 36.7)	6,850,000 (+ 15.1)

We have obtained many equally striking increases in other experiments. It is noteworthy that in Rabbit 5 the large increase in hemoglobin was not accompanied by a decided increase in the red blood cor-

puscles, showing clearly that the results could not be due to increased concentration of the blood, in which case the red blood corpuscles and hemoglobin would have increased proportionately. Blood smears stained with Jenner stain showed a large number of basophilic macrocytes. The blood smear also left no doubt that we were here dealing with a stimulation of the bone marrow. The animals which we have used fall into four groups:

1. Those which show an increase in both the hemoglobin and red blood corpuscles.

2. Those which show an increase in the hemoglobin without an increase in the corpuscles.

3. Those showing an increase in the corpuscles with no change in the hemoglobin.

4. Those showing little or no increase in either the red corpuscles or hemoglobin. The percentage of refractory animals (Group 4) is quite small.

An increase in the carbon dioxid in the atmosphere of the chamber with the normal oxygen concentration produces relatively little effect on the blood count in comparison with atmospheres poor in oxygen. We have some indication, however, that increased carbon dioxid here, as in the case of the respiratory center may stimulate the bone-marrow. In the case of the bone-marrow, however, the stimulation is slight whereas it acts powerfully on the respiratory center. It is interesting then that the respiratory center and the bone-marrow conduct themselves alike with regard to alteration in their own oxidative processes, since these two tissues provide the primary conditions for tissue oxidation. The work is interesting further in connection with polycythemia as observed clinically. It would seem that we might expect to find polycythemia in any chronic respiratory or circulatory condition which would result in the bone-marrow's receiving an insufficient supply of oxygen. In some of our experiments we have allowed animals to remain in the box at the normal oxygen concentration, and under these conditions, no increase in the red blood corpuscles and hemoglobin was noted. We have made certain observations in the box on the oxygen concentration required for a continuance of life, and compared with this the oxygen concentration required to support the flame of various combustible materials. It was shown by Clowes[20] that various combustible gases and liquids would burn only at definite minimum oxygen concentrations. We have confirmed certain phases of Clowes' work. Alcohol ceases to burn when the oxygen concentration falls to 15 per cent. The Madison illuminating gas ceases to burn in an oxygen con-

20. Clowes and Redwood: Proc. Royal Soc. London, 1894, lvi, 2.

centration of about 13 per cent. At about this point a flaming pledget of cotton saturated with ether is extinguished. The hydrogen flame is extinguished at about 6.6 per cent. oxygen. Below this point no combustible substances which we have studied will produce a flame. Animals continue to live, however, in an oxygen concentration far below this point. Thus we have found it necessary in order to produce alarming symptoms and death in rabbits to reduce the oxygen to between 3 and 3.5 per cent. This brings out one of the most striking differences between vital oxidation and ordinary combustion. If the atmosphere of the earth should become altered so as to contain only one-half the amount of oxygen, animal life would not be interfered with in any way, but it would be impossible to run a locomotive or to burn illuminating gas, and many of the substances which we consider dangerously inflammable would be as non-inflammable as water.

To return for a moment, before closing, to the original subject of the effect of physiologically active oxygen on inflammation and on immunity processes, I should like to refer briefly to two pieces of work. Prof. L. Hektoen[21] has investigated the effect of iodosobenzoate and iodoxybenzoate on certain immunity reactions. He injected these substances intravenously in dogs and found that they greatly increase the production of specific hemolysin following a single injection of 10 per cent. suspension of goat blood. The results were striking. The increase in hemolysin in the animals receiving the treatment was from 12 to 60 times as great as in the control animals. Iodbenzoate without active oxygen is without effect. Whether physiologically active oxygen will similarly stimulate the production of other immune bodies remains to be determined by further experiment. It is sufficiently obvious that if we could similarly increase the production of diphtheria antitoxin, it would be of great value.

Dr. S. Amberg and his co-workers[22] in a series of investigations have shown that iodosobenzoate and iodoxybenzoate injected intravenously or intraperitoneally have the power of markedly inhibiting the local inflammatory reaction as produced by mustard oil or bacterial toxins injected intracutaneously or instilled into the conjunctival sac, whereas iodbenzoate, possessing no physiologically active oxygen, is entirely without effect. The results are very striking indeed.

Many attempts of an unscientific character have been made to use oxygen in some form such as ozone, compressed air, etc., in the treatment of disease. I need only refer to the extensive and disastrous use of potassium chlorate internally which was in vogue for many years.

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21. Hektoen, L.: Tr. Chicago Pathological Soc., 1911, viii, 138.

22. Jour. Pharmacol. and exper. Therap., 1912, iii, 223; Jour. Am. Med. Assn., 1912, lix, 1598; Ztschr. f. d. ges. exper. Med., 1913, ii, 19, and oral communication.

It was supposed that since it is a very strong oxidizing agent outside the body that it would facilitate oxidation within the organism. This substance, however, does not lose its oxygen in the body, but is excreted unchanged in the urine. Dr. Abraham Jacobi[23] pointed out the great danger attendant on its use internally. The investigations which I have reviewed indicate that at some future time we may find important therapeutic applications of the results of studies in vital oxidation, but we hope that the next attempt will be founded on a basis of fact and will be subjected to careful scientific scrutiny before it is given to the profession.

23. Jacobi, Abraham: Tr. Med. Soc., New York, 1879, p. 365.

UROBILIN IN THE STOOL—AN INDEX TO BLOOD DESTRUCTION *

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This work was undertaken with the idea of determining whether the quantitative estimation of urobilin in the stool can be relied on to indicate the degree of blood destruction going on in the body, and also whether such estimation is of practical clinical value.

According to the theory most commonly accepted, urobilin is a decomposition product of bile, formed chiefly in the intestine by the action of putrefactive bacteria on the bile pigments. The quantity of urobilin in the feces does not represent the total amount of bile excreted into the intestine, for part of the urobilin is reabsorbed in the form of urobilinogen. Yet there seems to be a pretty constant relationship between the two, and the urobilin output may be taken as a rough measure of bile excretion. Since the amount of bile formed is, with a normal liver, directly dependent on the quantity of blood pigment brought to it, the variations in urobilin excretion may therefore be considered to indicate corresponding fluctuations in the amount of blood being destroyed.

The few investigators who have contributed to this subject are practically agreed in their results. Both Eppinger and Charnas[1] and Wilbur and Addis[2] state without reservation that an increased quantity of urobilin in the stool signifies an increased blood destruction. Simpson[3] who made many estimations on the stools of malaria patients, agrees with the above authors, and finds that the amount of urobilin excreted runs parallel with the intensity of hemolysis occurring during the course of the disease.

The method used was that employed by Wilbur and Addis,[2] which was found to be satisfactory and not too time-consuming. Briefly, the procedure consists in collecting the total twenty-four hourly amount of stool, protected from the light, emulsifying it in water, extracting a portion of this in a mechanical shaker with acid alcohol, next adding zinc acetate and Ehrlich's reagent, which bring out the spectroscopic

* Received for publication March 6, 1915.
* This work was carried on under a Dalton scholarship.
* From the Pathological Laboratory and the West Medical Service of the Massachusetts General Hospital.

1. Eppinger and Charnas: Arch. f. klin. Med., 1913, lxxviii, 387.
2. Wilbur and Addis: The Archives Int. Med., 1914, xiii, 235.
3. Simpson: Biochem. Jour., 1911, p. 378.

absorption bands of urobilin and urobilinogen, respectively. The solution is then diluted progressively till these absorption bands disappear and the reading made at this point. Thus the estimation, in terms of dilutions of the total twenty-four hourly stool, is really relatively quantitative.

As the daily variations in the urobilin output are often great, the following estimations represent an average of at least six days stools with very few exceptions, and often ten days or more. The normal excretion was determined in six individuals, four convalescent patients in whom there was no reason to expect abnormal blood destruction, and two normal persons. These varied from 2,000 to 8,500 dilutions. In none of the cases studied since, with a normal hemoglobin metabolism, has the urobilin reached 9,000. This figure, therefore, has been taken as the upper limit of normal average elimination. The normal given by Wilbur and Addis is practically identical with this.

Charnas used a very complicated and time-consuming method for extracting the urobilinogen from the stool and determining its amount by weight. The normal output in his cases averaged 0.13 gm. which would correspond approximately to 5,000 dilutions, the average normal in this series. On account of the instability of both urobilin and urobilinogen, and the difficulty of separating these substances out in pure form, no attempt is made here to translate dilutions into terms of weight.

Pernicious Anemia.—The eleven cases of group "A" all showed marked clinical evidence of increased blood destruction. In ten, the red count and hemoglobin were falling, and the eleventh remained about stationary. None were of the aplastic type. The highest readings were given by the four sickest patients, three of whom died. In striking contrast to these are the two cases of pernicious anemia in group "B" which were undergoing a rather rapid remission; the normal urobilin output during this phase of the disease being quite in harmony with the cessation of abnormal hemolytic activity.* This observation has also been made by Addis.[4]

Malaria.—The case of malaria was in an acute attack with a hemoglobin of 50 per cent.

Congenital Hemolytic Jaundice.—A very high urobilin excretion might well be expected in a hemolytic process severe enough to produce jaundice. Despite the evidence of great hemolysis, grave anemia rarely appears in this disease. This seems to suggest that in pernicious

* Urobilin in pernicious anemia as influenced by splenectomy, transfusion and salvarsan will be reported in a separate paper.

4. Addis: THE ARCHIVES INT. MED., 1915, xiv, 413.

anemia there is another factor besides hemolysis; perhaps a weak marrow function. This case gave the highest estimation of the series, agreeing with the results of two reported cases of Eppinger and Charnas.

TABLE OF CASES

A. CASES SHOWING AN INCREASE OVER NORMAL

	No. of Cases		Urobilin
1. Pernicious anemia	11		
Highest			30,000
Lowest			10,800
Average			21,800
2. Malaria	1		22,300
3. Congenital hemolytic jaundice	1		64,800
4. Secondary anemia—carcinoma (Regenerative type of blood)	1		22,000

B. CASES WITHIN NORMAL LIMITS

1. Pernicious anemia	2	a)	3,600
(Undergoing remission)		b)	2,600
2. Secondary anemia	6		
a. Bleeding hemorrhoids			5,900
b. Carcinoma of prostate			7,400
c. Carcinoma of stomach			2,900
d. Endocarditis			4,800
e. Tuberculosis			5,000
f. Septicemia			4,100
3. Grave anemia—questionably pernicious or early leukemia.	1		7,600
4. Leukemia	3		
a. Myelogenous			5,600
b. Myelogenous			6,400
c. Lymphatic			5,500
5. Biliary cirrhosis—jaundice	2		
a. Infectious type			2,700
b. Splenic (anemia?) type			6,000
6. Banti's Disease	1		2,800
7. Chronic passive congestion	2	a)	3,900
		b)	7,200
8. Pneumonia—jaundice	2	a)	8,800
		b)	3,300
9. Post-transfusion toxemia—jaundice. (Hemophilia)	1		1,400
10. Paroxysmal hemoglobinuria	1		4,200
11. Gastric ulcer—tarry stools	1		2,400

Secondary Anemia.—The one case of secondary anemia in group "A"—carcinoma of the stomach—had a large spleen and a blood which although compatible with a severe secondary anemia, showed marked evidence of increased bone marrow activity, i. e., a high color index, polychromatophilia, and blasts, from which one may infer that there was active blood destruction going on.

Case (a) of group "B" gave a history which would pass for pernicious anemia and showed a blood picture strikingly like that seen in this disease, i. e., a color index above 1, polychromatophilia, macrocytes, etc., except that many of the red cells showed definite achromia. It was found that he had internal hemorrhoids which had bled at times since the onset of the present illness, but never very much, nor was the increase in anemia associated with any increased bleeding. The

normal urobilin output, however, was strongly in favor of this being a secondary anemia. Treatment was directed toward eliminating this possible etiologic factor with the result that within three weeks after operation on his hemorrhoids, the anemia had almost disappeared.

Case (b) showed a somewhat changing blood picture. Two months previous to admission a relative and absolute lymphocytosis had been found. During his first stay in the hospital the blood was indistinguishable from that seen in pernicious anemia and he was discharged with this diagnosis. *The normal urobilin output found in this case was against pernicious anemia.* After a few weeks he entered the hospital again in a poorer condition and with marked dyspnea. The only changes in the blood were a marked increase in the number of normoblasts—as high as 70 per cent. per 100 white cells—and the presence of an occasional myelocyte. At this time an enlarged and nodular prostate was felt and X rays of the bones and lungs gave a picture strongly suggesting diffuse metastatic malignant disease. Our final diagnosis of carcinoma of the prostate with extensive bone marrow involvement would explain the very unusual blood picture as well as the anemia of a nonhemolytic type. For, according to Dr. J. H. Wright, the replacement of his red bone marrow by metastatic tumor tissue produced not only the anemia, but also caused hematopoiesis in the liver and spleen and consequently a fetal type of blood, i. e., large numbers of normoblasts in the circulation.

The remaining four cases in group "B" all showed a diminution in blood production—a low color index, achromia and no blasts.

Grave Anemia.—Questionably pernicious or early leukemia. This was another case of atypical anemia diagnosed as pernicious during life. The blood picture was in every way characteristic of this disease; however, several weeks before death the spleen began to enlarge and within a short time had filled the entire left side. At autopsy the glands were found to be filled with myelocytes and the spleen and bone marrow showed large areas of myelocyte formation.

Leukemia.—All three cases were treated with radium at the Collis P. Huntington Memorial Hospital and in two the urobilin was determined before and during the course of the treatment. Of particular interest is the fact that during the three weeks of radium application, the white count in one dropped from 640,000 to 94,000 and in the other from 700,000 to 340,000, yet the urobilin remained the same, instead of increasing as might be expected, and the red counts showed an upward tendency. The absence of any change in urobilin output shows conclusively that radium does not destroy red cells, but rather

stimulates their formation. It would be difficult to demonstrate in any other way that the increased red cell production was not accompanied by an increased destruction which might have acted to stimulate the bone marrow.[5]

Biliary Cirrhosis.—The low figures in these two cases are of interest in view of the increased urobilin output which Eppinger found in hypertrophic cirrhosis. All clinical evidence supported the normal estimation to prove that the jaundice present was of hepatic and not of hemolytic origin.

Case "B" called "splenic" in type, for want of a better name, as there was marked enlargement of the spleen without apparent etiology or accompanying anemia, gave a history which might well have passed for one of congenital hemolytic jaundice. Yet the slight enlargement of the liver, the presence of bile in the urine, the absence of increased fragility, and the small percentage of reticulated cells, together with the normal urobilin output, definitely excluded abnormal blood destruction as the cause of his jaundice.

Banti's Disease.—There is no uniformity in the degree of blood destruction occurring in Banti's disease. Certain cases, or possibly stages, of the process show an increase, others do not. It is impossible to say as yet what these variations signify, since there are such a small number of reported cases of Banti's disease in which urobilin estimations have been made. Eppinger, however, who has studied the disease from this point of view, has the feeling that those cases which gave high urobilin estimations showed the most favorable results after splenectomy.

Chronic Passive Congestion.—There was no reason to suppose that an increased urobilin output would be found in this condition. I made the estimations on these patients because Eppinger and Charnas have reported high figures in chronic passive congestion. A possible explanation of this discrepancy in results may be the fact that their two cases were evidently *in extremis,* while those in the above table had well marked decompensation but were not dangerously ill.

Pneumonia.—If the jaundice present in these two cases were of hemolytic origin, one would expect the urobilin to be somewhere in the neighborhood of the estimation shown by congenital hemolytic jaundice. That it was within normal limits seems strong evidence in favor of a hepatogenous origin.

5. The effect of radium on the blood in these cases, and also the findings in the case of "grave" anemia are cited by the kind permission of Dr. Thomas Ordway.

Post-Transfusion Toxemia—Jaundice.—This was a patient with hemophilia who had a severe reaction after transfusion, followed in thirty-six hours by a moderate jaundice and almost complete suppression of urine. At first sight it seemed that a marked hemolysis had occurred. However, there was no increase in the anemia present before transfusion, the urine obtained on the second day contained bile and urobilin but no hemoglobin, and jaundice persisted for ten days, when death supervened. The low urobilin output added valuable information, and, together with the above facts, made it apparent that the condition was a toxemia affecting the liver and kidneys especially and that the jaundice was due to marked hepatic insufficiency. Autopsy showed central degeneration of the liver lobules and acute interstitial nephritis.

Paroxysmal Hemoglobinuria.—Paroxysms were produced in this patient several times, and in spite of the very evident free hemoglobin present in the blood serum afterwards, the urobilin output was not increased. This rather puzzling condition was explained by determining the rate of hemoglobin excretion by the kidneys, which was found to be exceedingly rapid—over 90 per cent. of the hemoglobin set free was eliminated in the first two hours.[6]

Tarry Stools.—These stools were selected in order to determine whether the blood pigments in cases of increased hemolysis might not pass into the intestine as such, and there be broken down directly into urobilin, without having to go through the intermediary stage of bile formation. If this were the case, blood in the stools would be a serious factor of error in urobilin determinations. The low readings here rule out this possibility.

SUMMARY AND CONCLUSIONS

1. An increased quantity of urobilin in the stool was found constantly in 11 cases of pernicious anemia (except during remission); also in congenital hemolytic jaundice, malaria, and in one case of secondary anemia with a regenerative type of blood. All these cases showed clinical evidence of increased blood destruction.

2. Cases of leukemia, secondary anemia, chronic passive congestion, pneumonia with jaundice, and diseases of the liver, all showed a urobilin output within the limits found in normal individuals.

3. Those patients in whom the evidence of blood destruction was most marked, gave the highest urobilin estimations.

6. A more complete report of this case will be made later.

4. There was no case with a normal urobilin output which showed any evidence of abnormal hemolytic activity.

5. In view of the consistency of the above results, it seems fair to conclude, first, that the quantity of urobilin in the stool may be taken as an approximate measure of the degree of hemolysis occurring in the body, and second, that such estimation is of very definite clinical value in the diagnosis of conditions questionably hemolytic in character, particularly in anemias of uncertain type.

THE EFFECT OF REPEATED INJECTIONS OF FOREIGN PROTEIN ON THE HEART MUSCLE *

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During some investigations previously reported,[1] dealing with the effect of repeated injections of foreign protein on the kidneys and liver of experimental animals, it was noted that changes frequently occurred in the heart muscle; and at that time mention was made of this fact. Since then the study of chronic protein intoxication and the effect of repeated anaphylactic shocks in animals, has been continued, and as one part of the investigation especial attention has been paid to the change in the myocardium.

That certain disturbances in the function of heart muscle may accompany acute anaphylactic shock is already well established. Auer and Robinson[2] have observed in both dogs and rabbits, marked alterations in rhythm, delay in the conduction of impulse from auricle to ventricle and partial or complete block during the acute phase of anaphylactic shock. Auer[3] also describes a waxy appearance of the myocardium and of the voluntary muscles of the leg in rabbits dying under the same conditions.

Worzekowsky and Kundratitz[4] have observed swelling, granulation and loss of cross striation in the muscle fibers of the heart following acute anaphylactic shock in guinea-pigs, while much the same changes are described by Beneke and Steinschneider.[5]

The details of the technic for these experiments are fully described in the previous article. Suffice it to say that rabbits, dogs, cats and guinea-pigs were sensitized to egg-white alone, horse serum alone, or to both proteins, and after an interval of three weeks inoculated with intoxicating doses of these foreign proteins. An attempt was always made to administer a dose sufficiently large to produce symptoms, but not large enough to kill.

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* From the Medical Clinic of Columbia University, Presbyterian Hospital, New York.

1. Longcope, W. T.: Jour. Exper. Med., 1913, xviii, 678.

2. Auer and Robinson: Jour. Exper. Med., 1913, xviii, 42.

3. Auer: Ztschr. f. Physiol., 1913, xxviii, 383.

4. Worzekowsky and Kundratitz: Arch. f. exper. Path. u. Pharmakol., 1913, lxxiii, 33.

5. Beneke and Steinschneider: Centbl. f. allg. Path., 1912, xxiii, 592; Ztschr. f. allg. Path., 1914, xxiv, 415.

The sensitizing doses were given at times intravenously (except in guinea-pigs), at times intraperitoneally and occasionally subcutaneously. The intoxicating doses were administered either intravenously or intraperitoneally. The number of intoxicating doses varied from three to twenty. In the majority of cases the animals received six to twelve intoxicating doses at intervals of one to two weeks.

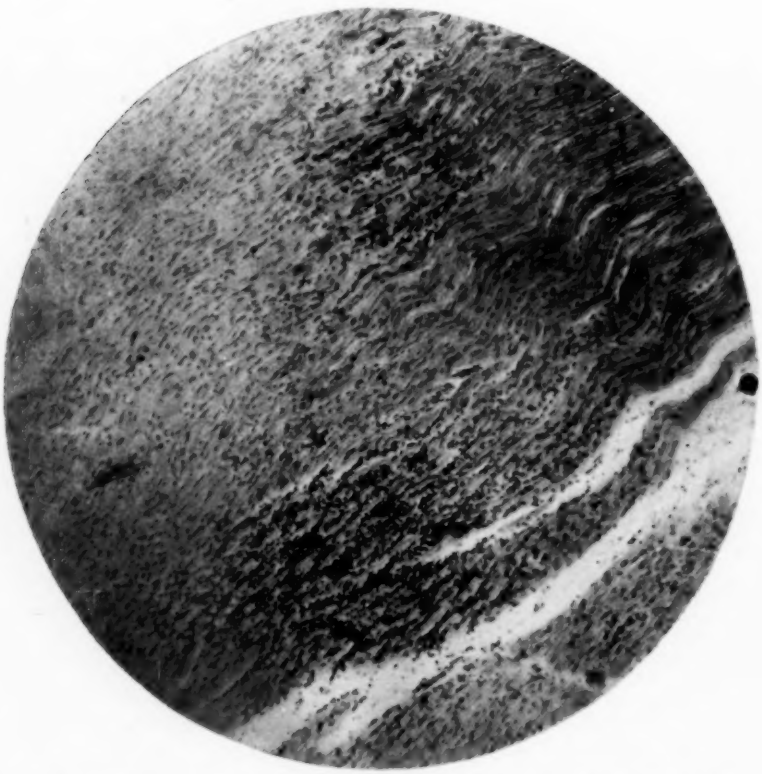

Fig. 1.—Rabbit 24. Effect of repeated injections of egg white on heart of sensitized rabbit. Extensive focal infiltration of myocardium by small round cells.

As controls many hearts from rabbits and guinea-pigs that were supposedly normal have been examined, and a moderate number of hearts from dogs and cats. As a part of the study, rabbits have also been inoculated with a single dose of horse serum or egg white and their organs examined after varying intervals of time.

The material comprises the organs from 54 rabbits, 33 of which were sensitized and later received repeated intoxicating injections of foreign protein, 22 of which received but a single large dose of foreign protein; and 11 guinea-pigs, 13 dogs and 10 cats, all subjected to repeated anaphylactic shocks.

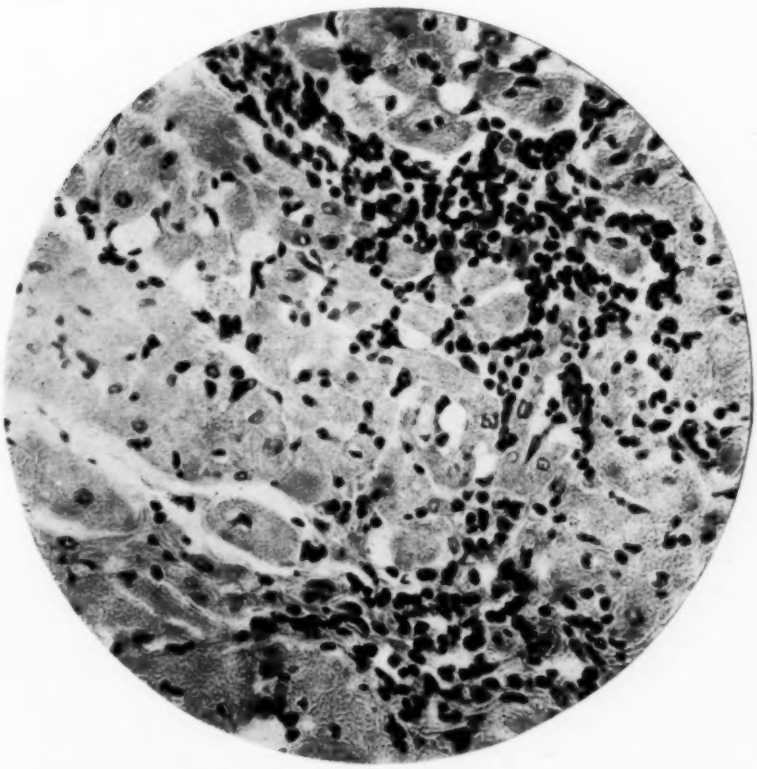

Fig. 2.—Rabbit E. I. Effect of repeated injections of egg white on myocardium of sensitized rabbit. Small focus of round cell infiltration. (High power.)

Since the changes in the myocardium are confined almost exclusively to the rabbit, these alone will be described in detail.

Of 11 guinea-pigs, 3 showed the myocardial changes to be described; of the 13 dogs one, and of the 10 cats one, whereas of the 33 rabbits subjected to repeated anaphylactic shock, 27, or 81.8 per cent., showed more or less extensive involvement of the myocardium.

Macroscopically the hearts presented little that was abnormal. In a few instances they seemed large and were dilated, but since no

accurate weights or measurements were taken, little importance can be attached to this. Frequently the heart muscle was pale or showed a slight grayish streaking, and in a few instances it was distinctly firm. Microscopically the alterations were very definite and often widespread. They were seen both in the right and left ventricle and in the auricle. Sometimes they appeared more intense in one situation than another and were particularly common and numerous in the right ventricle.

What appeared to be the earliest and certainly the smallest lesions consisted of foci in which the muscle fibers looked swollen but showed no other definite changes. Surrounding these fibers and infiltrating irregularly the reticular spaces between them, were considerable numbers of small round cells. In the larger and further advanced lesions the muscle fibers presented more definite changes indicative of degeneration. There was swelling, loss of striation, occasionally vacuolization or irregular staining of the sarcoplasm. The nuclei were swollen and took the hematoxylin stain poorly. In marked contrast, however, to these comparatively slight alterations in the muscle fibers, was the extensive infiltration of small round cells which was always present. About the margins of the degenerative muscle fibers they were densely packed and infiltrated between the muscle cells in great numbers. So large and dense were many of these foci that they could be seen by the naked eye in sections stained by hematoxylin and eosin, when they stood out as sharply marked blue points. In the foci where the infiltration was most pronounced the degeneration of the muscle cells was most marked. Here and there the fibers in cross section showed as an indefinite, shrunken mass of protoplasm, staining rather deeply in eosin. Rarely the fibers had disappeared entirely.

In the most advanced stage of this subacute process, the focus appeared as a mass of small round cells, amongst which were scattered the remains of the muscle fibers.

What was taken to be the final stage of this focal chronic inflammatory process was a group of swollen, irregular vacuolated muscle fibers embedded in a mesh of connective tissue, infiltrated here and there with small round cells or epithelioid cells.

The lesions which have just been described were seen in all parts of the heart muscle. They occurred beneath the endocardium, especially of the right ventricle, as well as in the depths of the muscle. They were rarely, if ever, situated about blood vessels, and the smaller arteries as well as the capillaries within and surrounding the foci were normal. Thrombi were never observed.

As a rule the heart muscle between these foci and a short distance from them was normal, though in the right ventricle especially there was occasionally to be seen some edema and slight diffuse infiltration

of small round cells. In the latter stages of the process, too, when the cellular infiltration was largely replaced by connective tissue, the margin of the focus was not well defined and when many such areas occurred the appearance, especially in the right ventricle, was that of a more or less diffuse interstitial myocarditis.

One may characterize these changes, then, as a slowly progressing degeneration of muscle fibers in isolated foci, accompanied very early by an intense round cell infiltration, and finally healing as connective tissue scars. They are not associated with discoverable changes in the blood vessels or capillaries. They vary in number from one to seven or eight in a single section and in size from the involvement of a few muscle fibers to foci measuring 0.5 to 1 mm. in diameter.

Though a great number of hearts from normal rabbits have been carefully studied, no such changes have ever been observed. Indeed, in one lot of thirty-six rabbits which were used for some of these experiments, all arriving at the same time from a single dealer, twelve were killed as controls and the hearts of all were normal. It seems justifiable, therefore, to conclude that the lesions which have been described are in some way dependent on the introduction of foreign protein into the circulation of these animals. The total absence of thrombi or vascular abnormalities excludes the possiblity of capillary thrombosis as a cause.

To compare the results obtained in sensitized rabbits subjected to repeated anaphylactic shocks, the hearts from twenty-two rabbits which had received but a single dose of horse serum or egg white, or at most three injections repeated at twenty-four to forty-eight hour intervals, were examined at varying intervals after the injection had been made. This experiment revealed the fact that occasionally these animals showed the same changes as those repeatedly inoculated. Thus in this series of twenty-two animals the hearts of eight rabbits, or 25 per cent., showed similar but much less marked changes. The foci of degeneration and infiltration were fewer, so that often only one or two could be found after searching through several sections, and they were much smaller. This observation is sufficient to show, however, that subacute inflammatory foci do occur in the heart muscle of rabbits after a single injection of egg white or horse serum.

This brings up the question as to whether the alterations described are dependent on a primary toxic action of foreign proteins when introduced parenterally on the cells of animals, or whether the lesions are dependent on an injury which occurs only during the period of anaphylactic shock. In a later publication this question will be fully dealt with, but suffice it to say at present that the occasional appearance of the lesions indicated in animals receiving but a single injection

of a large amount of foreign protein, does not justify the assumption that the entire process is caused by the primary toxic action of the foreign protein. In man, at least, the single injection of a foreign protein is followed, in many instances, after an interval of seven to ten days, by "serum sickness," a condition often of severe intoxication which von Pirquet and Schick have shown to be an anaphylactic phenomenon. Though the symptom complex known as serum disease is not observed in animals, it is still possible that an analogous condition accompanied by an injury to certain cells of the body may follow the single injection of foreign protein in any animal.

It is well known that the injection of certain toxic substances will produce extensive myocarditis in rabbits. Epinephrin and spartein have been shown by Loeb to bring about alteration in the heart muscle of rabbits. These changes, however, are entirely different from the ones obtained in my experiments.

Perhaps more nearly allied, but still not identical, are the focalized degenerative and productive lesions obtained by several observers in the hearts of rabbits after the intravenous injection of certain types of streptococci. Thalheimer and Rothschild[6] have recently reviewed the literature on this subject and have described quite accurately such myocardial changes. The lesions thus produced differ principally from those that I have obtained in the degree of necrosis of the muscle fiber and polymorphonuclear leukocytic infiltration, which in my sections was entirely absent.

CONCLUSIONS

Repeated intoxicating injections of foreign proteins in rabbits previously sensitized to these substances causes extensive focal degeneration of the cells of the heart muscle as well as of the kidney and liver. In the heart muscle these areas are characterized early by a dense infiltration of small round cells. Later the foci of subacute inflammation give place to scar formation, so that in some instances the appearance of interstitial myocarditis is produced.

Though these changes in the myocardium are only widespread and only occur regularly after repeated injections of foreign protein in sensitized animals, they may occasionally be found in rabbits that have received a single injection of foreign protein.

This does not necessarily mean that the protein is primarily toxic for the cells of the animal.

The lesions are quite different from those produced by injections of epinephrin and do not correspond exactly with the descriptions of those obtained from injections of streptococci.

680 Madison Avenue.

6. Rothschild and Thalheimer: Jour. Exper. Med., 1914, xix, 429.

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